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of the

AMERICAN SURGICAL ASSOCIATION

AT HOT SPRINGS, VIRGINIA

MARCH 25, 26 and 27, 1947

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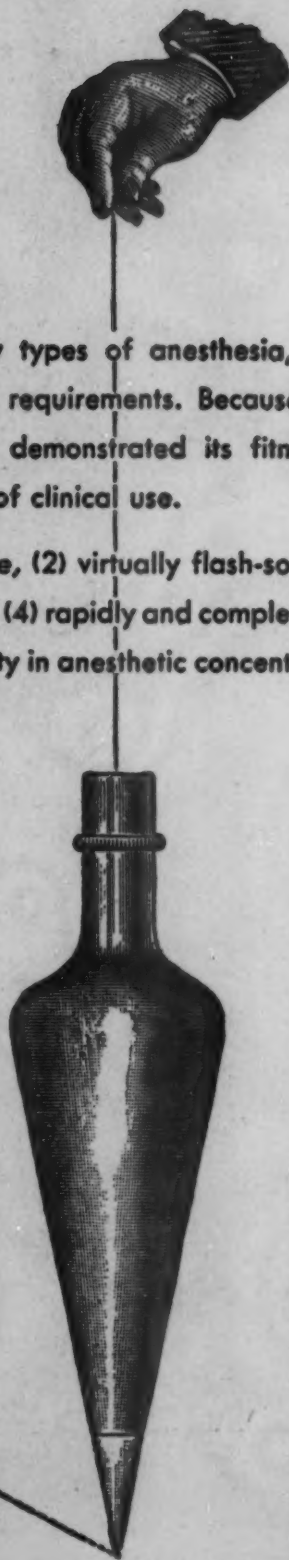
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TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION

MEETING HELD AT HOT SPRINGS, VA.
MARCH 25, 26 and 27, 1947

ADDRESS OF THE PRESIDENT SCIENCE AND HUMANISM IN SURGERY*

EDWARD D. CHURCHILL, M.D.

BOSTON, MASSACHUSETTS

"I will impart this Art by precept, by lecture, and
by every mode of teaching."—Oath of Hippocrates.

IN THE AUTUMN OF A. D. 9 the German hero Arminius fell upon Quintilius Varus in the shades of Teutoberger Forest and destroyed three of the finest legions of Rome. The bold victory forced the Romans to withdraw their frontier from the Elbe to the Rhine. This event brought down what now might be called an iron curtain between the Germans and the Graeco-Roman civilization. To imply that this curtain actually led to the development of a Germanic culture and science separate from that of the rest of Europe would be an error, for during many centuries wars and religious disputes swept across the entire continent of Europe, leveling cultural and scientific barriers. This very error, the concept of a separate Germanic culture, was partly a cause and somewhat a symptom of the rapidly moving events of the present century that culminated in the total destruction of Germany. Nevertheless, American Surgery as we know it today has developed from the union of two quite different streams, and the origins of these may be traced to opposite sides of this ancient iron curtain along the Rhine.

The stream from Germany was a turbulent freshet of Science, beginning in the middle of the nineteenth century and reaching full flood by 1914; now

* Address delivered before the American Surgical Association, March 25, 1947, Hot Springs, Virginia.

nothing of its source is left but a dried-up watercourse. The broad river into which it poured had more distant origins in the ancient watershed of Graeco-Roman medicine, and reached the American Colonies from England and France. This was a leisurely moving current, rich in the humanitarian traditions of the Christian Church but, like the Church, burdened with dogma and superstition. Emergent leaders, from time to time, introduced scientific concepts of startling novelty and import; but the potential power of a new Medicine guided and nourished by Science had not been envisioned.

The junction of the freshet of Science with the broad and ancient river produced currents and countercurrents in American Surgery that are still visible today. Had the content of Surgery been pure Technology, on the one hand, or pure Science, on the other, the mingling of the streams would have occasioned no disturbance; the contribution of the Germanic freshet would have been received quietly into the volume flow of the river. To understand the troubling of the waters, it is necessary to examine Surgery closely and define its content and its function. It is also necessary to consider the organizational patterns through which its content is converted into dynamic function. First I shall consider what may be called the Content of Surgery.

Surgery is in large part a handicraft with elaborate technics that may be grouped as Technology. But it transcends Technology in the desire and responsibility to find safe application of these technics to the needs of humanity. This quality, which distinguishes a profession from a trade, may, for lack of a better term, be designated as Humanism and identified as one of the basic contents of Surgery. Historical documentation might be required to convince certain purists that Surgery can rightfully identify another of its component parts as Science. As the argument would require precisely drawn definitions, I shall not belabor the issue but boldly stake out a claim and defend it, if necessary, at some future time. In addition, if one be honest in this analysis, he cannot fail to see that Surgery is seeded with *ad hoc* hypotheses, or, in more frank terms, empiricisms and irrational beliefs. These four components, Technology, Humanism, Science, and Empiricism, form what may be called the Content of Surgery. This differs from the Content of Internal Medicine only in the greater range of surgical Technology.

In common with all professions, Surgery expresses itself in Dynamic Functions. These, considered broadly, are three in number: Cure of Disease (action), the Strengthening of the Skill to Cure by Progress (growth),* and the Perpetuation of the Skill to Cure by Teaching (reproduction).

The Content of Surgery is transformed into the Dynamic Functions of Surgery by means of various Organizational Patterns. These patterns, at least in recent times, have been various combinations of the Hospital, the University, and the State—including in the State, agencies within the framework of

* I have deliberately avoided use of the term "research." Progress in surgery may result from a wide range of effort that extends from the employment of common sense and logical thinking to the use of the well-controlled experiment designed to answer a precisely formulated question.

government and agencies designed to administer social forces independent of government.

Having dissected Surgery in this arbitrary manner in an attempt to bring some clarity of thinking to the subject, I shall turn to the historical approach, and choose examples chiefly from Teaching. Major trends in surgery that alter the relative emphasis placed upon those abstractions that I have called its Content are foreshadowed by changes in Teaching. The reason is obvious, because only an oncoming generation has sufficient weight to shift the emphasis to a significant degree; furthermore, the teachers of any profession are likely to be sensitive to an approaching change and, being articulate, herald its approach. The pursuit of this cockcrow responsibility by teachers always has annoyed the profession at large. But medical education will remain a controversial subject just so long as Medicine itself is open to change.

In selecting examples from the history of Teaching, I have chosen ones that will record the advent of Science and also certain ones to reveal the content of Humanism that resides in Surgery. The controversies, as usual, have not dealt with basic problems, but have centered on organizational patterns, particularly those formed by University and Hospital. These patterns are unimportant in themselves; they achieve significance only as they succeed or fail to transmit with fidelity the total Content of Surgery. The University is selective in its response to the wave lengths of Science; the Hospital is selective in the expression of Humanism. In view of an ever-changing Content, it is not surprising that a perfect instrument as yet has not been achieved.

The Germanic influence in American medical education was not apparent until the rise of scientific medicine in Germany in the middle of the 19th century, and so a background must be sought in the situation in Britain during the 17th and 18th centuries.

Only a beginning was made in 17th century Britain to displace the entrenched classicist methods in medical education.¹ The traditions of Oxford and Cambridge were essentially conservative. Medical studies at Cambridge were governed by the Elizabethan statutes of 1570. The Caroline Code of statutes was instituted at Oxford in 1636 and strictly regulated medical studies at that University. Oxford was permitted to grant a surgeon a license to practice throughout England after he had shown "skill, honesty and repute in that art" for seven years. "He must have performed two anatomies, made at least three cures and been approved by three doctors of the University, or by the Regius Professor and one other doctor. Upon graduation he promised to cure four paupers gratuitously and not to overstep the bounds of his own art by attempting to practice medicine. Furthermore, he gave his word that he would 'not ask too much salary, or delay any cure with the view of later gain.'" ² The efforts of the universities in medical education were not looked upon with favor by the great practitioners of that day, who taught the art by the apprentice system. "Physick," says Sydenham, "is not to bee learned by going to universities, but hee is for taking apprentices; and says one had as good send a man to Oxford to learn shoemaking as practicing physick."³ "A

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Doctor bred up in the Contemplative Philosophy of the Schools, may be a Scholar and a very fine Gentleman; but what is that to the curing of a Disease, or the rousing of a Heart-sick Man from his bed of Languishment?"⁴

Compared to that of the universities, the situation with respect to hospitals was even worse. The action of Henry VIII that swept away the medieval hospital system of England in the name of the Reformation has been interpreted as an effort to abolish the extravagances of the ecclesiastics. Whatever the motive, this harsh decree was followed by a period of misery and confusion that lasted nearly two centuries. Then a new philanthropy was born that was destined to express itself through a practical and concrete charity and bring a new concept of the hospital to the world. Whether or no the panic of the Great Plague was immediately responsible, there came a "revival of charity with all the old touch of romance which characterized it in the Middle Ages."⁵

The Crown first tried its hand in the new philanthropy, but its benevolence was inadequate and the administrative control measures it established proved harassing. Then in the 18th century came the magnificent rise of the voluntary general hospital that formed the pattern for the first hospitals of our new world.

The first organization of medical teaching in this country took place in Philadelphia in 1765. John Morgan (1735-89) had been recommended by John Fothergill, a physician of London, as being qualified to teach. Morgan, a graduate of Edinburgh in 1762, had worked under William Hunter and the Munros. In a letter to John Warren in 1785, Morgan showed an awareness of the significance of the medical sciences, that were then but weak, ancillary forces in education. "Medicine," he stated, "is a science as important in its object as it is difficult in the acquisition. It is very extensive in its researches, and presupposes the knowledge of many other sciences. The cultivation of it requires no small abilities, and demands of those who engage in the arduous pursuit an enlarged and benevolent mind."

But there were too many pressing problems in the days of the Revolution to give time to the cultivation of the science of medicine. Morgan himself, in 1775, was appointed "Director General and Physician in Chief" of the American Army. Packard, in describing the Army medical service of those days, writes: "The surgeons were without any definite authority, absolutely destitute of any medical or surgical supplies, except those provided by private means, and in many cases as ignorant and ill-educated men as could well have been found." According to Garrison, Morgan "entered upon his duties with vigor, insisting upon rigorous examinations for medical officers and subordinating the regimental surgeons to the hospital chiefs." But the politicians, both professional and lay, soon had his head and he was dismissed by Congress in 1777.

The early medical schools merely supplemented the training given by the apprenticeship method. The courses of lectures were only nominally under university control, and although dignity was sought through the sanction of a university, they existed wholly for the interests of the professors. "Students in small classes of two or three lived in families of surgeons, studied methods, followed their cases, compounded their drugs, did their chores and received a

certain amount of personal instruction."⁶ The pace of learning was slow and the ultimate attainment not great, even though eventually the apprentice might absorb all that the instructor had to offer.

During the last century many of the developments in this country were shaped by the rapid expansion of population in a tremendous geographic territory. As a result of the demand for doctors, the inevitable happened. "Loose and shifting bands of practising physicians, calling themselves a faculty, tried to impart, chiefly by lectures, to heterogeneous, uneducated groups of students the empirical knowledge—sound and unsound—which they themselves possessed. First and last, American towns have produced over 400 such medical schools. The teaching of medicine on these terms was, directly, in cash, and indirectly, in prestige, a profitable business."⁷ Proprietary medical schools have been defined by Zinnser as "privately founded corporations of groups of physicians and surgeons who organize courses without a well-conceived educational plan."

Henry Jacob Bigelow was appointed Professor of Surgery in 1849. He had studied long in Paris and had journeyed weekly to London to hear Paget. In accordance with his time, he deemed the didactic lecture paramount. The operating room was the theater in which he excited the astonishment and admiration of his students. Bigelow has been introduced at this point as a concession to chronology. I will leave him busy with his didactic lectures—unaware of the floodwaters that were arising in Germany, destined to descend on the well-regulated little world of surgery that was so firmly under his control.

The story begins in Germany during the last years of the 18th and the first decades of the 19th century, when German philosophers—particularly Kant (1724–1804) and Schopenhauer (1788–1860)—provided a powerful impulse to science in the universities of that country. "That was a most resplendent epoch, but so little was it a function of a certain people or race that it passed; it passed like the Hellas of Pericles, the Italy of the Renaissance, the France of Louis XIV: human history makes efforts like these, in which a flowering of men of genius comes to the world, only at intervals of centuries or millennia."⁸ Philosophical thought was already declining by 1830, but the united and imperial state fostered a period of industry and achievement in German universities that flowered in research in the natural and medical sciences. The wealth and importance of Germany's intellectual and technical achievements made it a country to which our students turned as the fountain-head and guide of medical science. This was, in all, a brief period, 1850–1914, but its impact on medicine and medical education has been enormous. To trace the effect on American medicine, I shall sketch the career of one of the first American students to enter Vienna, Dr. James C. White.

In 1853, four years after Bigelow became Professor of Surgery, J. C. White, of Belfast, Maine, started his course in medical studies. To complete the background it is necessary to hear his own story about the medical studies in Boston that prepared him for his work abroad.⁹

"Coming from the preparatory fitting of the public school or academy, or

from college, the medical student of those early days had but small choice of medical schools . . . from which he might receive his professional degree. This might be acquired, by entering his name with some physician and purchasing professor's tickets at two winter courses of lectures, in two years' time, after a final and farcical examination. These were the minimum requirements to turn a rough country boy into a doctor authorized to practice medicine in those days. There was no obligation to attend a single exercise during the medical school course of lectures lasting three or four months, or to receive any manner of instruction from his nominal instructor during the remainder of the year.

"What did Harvard University offer the student of medicine at that time? Its Medical School consisted of seven professors. . . . They had entire control of the affairs of the school. They sold their individual tickets of admission to their respective courses through a business agent, and every candidate for a degree was obliged to buy them all for at least one year. The purchase of a similar set of tickets in any other reputable medical school was accepted as the equivalent of a second course of lectures at Harvard. The exhibition of a certificate of having entered one's name three years previously with some practitioner, the preparation of a thesis on some subject in medicine, and answering the simple questions put by each professor in turn, for seven minutes each, equal to a total of one and a half hours, constituted the only and final method of examination as to the fitness of a candidate for a degree. If he received the favorable votes of a majority of the board—four—he became a Doctor of Medicine, and that degree carried with it authority to practice in Massachusetts. The lectures began at eight in the morning and continued until one o'clock, five consecutive hours on some days of listening for the conscientious student without interruption save for the five minutes' intermission between them. They were repeated without change each year. Twice a week there was a clinical medical visit at the Massachusetts General Hospital of one hour, which the whole class of 127 students attended, filling the ward—of whom but 31 held a college degree. On Saturdays there was a similar visit in the surgical wards, followed by operations in the amphitheatre under the dome for an hour or two. . . . There was no graduation of studies, the whole body of students attending each lecture from first to last together. There were no laboratories, no private courses, no individual instruction—no student looked into a microscope or handled a test-tube."

Having completed his medical course in the spring of 1856, young White was obliged, if he desired a more adequate education, to seek it abroad. His decision to go to Vienna was an important event; how he came to make it is of interest.

"Paris had long enjoyed the reputation of holding the highest rank as a school of medicine, both in her renowned teachers and the clinical advantages she possessed. . . . But a change was beginning. Gradually the philosophic German mind, so skeptical and irreverent as to accept no dogma unchallenged, and so patient and industrious in following the suggestions of nature to their

source, began to make itself felt. This influence soon became an acknowledged power as the careful observation of devoted students—men who cared for nothing else in life than their studies, who had no higher ambition than their scientific reputation, who knew no other pleasure than was to be found in the laboratory or hospital, and who never aspired to become rich — became known. . . .

"Dr. Calvin Ellis, just returned from Europe . . . had spent a few weeks in Vienna and . . . advised me," writes White, "to make it my first and chief place of study. . . . At that time few American or English medical students visited Vienna. I was the first of the former, I believe, to spend a full year there, and there were but four or five others during my residence there, for the fame of its incomparable teachers . . . had scarcely spread to America or England." So in August, 1856, White embarked in the *City of Washington*, a ship-rigged, side-wheel steamer, running between New York and Bremen, and after 14 days arrived at the latter city.

As I am concerned only with the broader aspects of changes in medical education, it is beyond my purpose to record the detailed history of the reforms of the last half of the last century. Adequate illustration is afforded by following Doctor White after his return from Vienna. In 1866 editorials from his pen appeared in the *Boston Medical and Surgical Journal*. These were regarded as rank heresy by his colleagues, and he was advised to restrain his zeal.

"Not until the profession throughout the country," he wrote, "shall awake to the deplorable deficiencies of our present system and shall insist upon the establishment of some uniform standard . . . can medicine in America raise itself to a level with that of foreign countries, or even with other branches of learning at home.

"Very little can be accomplished in this direction by any one school, however desirous its government may be of reform; for any unusual severity in its examinations or length of study required would turn its students to other and easier places and prove its own ruin. How far, for instance, would the cause of medical education be advanced if Harvard University . . . should refuse a degree until after four years' study . . . while the Medical Department of Yale College continues to confer the same right to practise . . . at the end of two years only, and issues a circular containing such a statement as this: 'Experience has shown that a large proportion of the whole field of medical investigation, embracing most of the important topics, can be comprised in a single course of lectures, by avoiding that extreme variety of subjects and minuteness of detail, which are so apt to confuse and oppress the mind of the learner, and render the knowledge acquired superficial and vague, rather than clear, definite, and well fixed.' When an institution of this rank so lowers the tone of scientific study, what can we expect of the great number of private schools all over the country licensed to make doctors by State Legislatures?"

In 1870 Doctor White, then a distinguished member of the Harvard faculty, delivered the Introductory Address at the opening of the winter course

of lectures. "President Eliot, who had recently been appointed to that high office, to whom I read my address in advance, said he would take measures that I should have a good audience, and so at noon on November 2, I found the large lecture-room of the Medical College filled with the students and many members of the governing bodies of the University. The invited guests assembled in the Warren Museum above, and there Professor H. J. Bigelow said to me: 'Well, White, now we are about to catch it, I suppose.'"

The address itself will bear reading and rereading today, and time allows but limited direct quotation:

"To those who have received no advice upon these matters . . . I would say, devote the largest part of your time to anatomy, physiology and chemistry. . . . These branches are the groundwork of the art of medicine, and it is in these that students generally fail in thoroughness, and therefore as physicians fail to know their art through life. . . .

"By such beginnings you will gain the taste and courage for that independent work in later years which will distinguish you from the ordinary practitioner. I do not mean to say that you should take absolutely no share in any of the other exercises of the school, that you should not attend operations and occasionally visit the hospital, and see an autopsy, and perhaps study surgery and materia medica; but the less of these and the more of the others the better. A single year's attendance upon the advanced branches after such a preliminary training will give you a far deeper knowledge of them than one gets by a three years' course pursued without system or given wholly to the so-called practical or special branches."

"There is no such contemptible spirit among students as . . . preferred attention to such parts of their studies as seem to have a practical value. It exhibits itself in attendance upon the lectures relating to the practice of medicine . . . in the production of the note-book only when the word 'treatment' is mentioned . . . and in the neglect of all that raises medicine to the rank of a science and its followers to be learned men. It degrades the art to the level of a mere trade."

". . . nine-tenths of all that is new and important in physiology, pathology, and medical chemistry, is the work of German hands and brains, and is given to the world in their tongue."

"So long as it is held that there is a demand for cheap doctors in this country . . . so long we shall make poorly educated doctors and nothing else. . . .

"Until we renounce the theory that medicine in America is to be taught, not as a science as elsewhere, that only so much of it is to be served up to the student as will make him a good practising doctor, and that he has no share in its future progress as an independent worker in its deep places, we need not hope for better things. . . .

"We do not sufficiently honor our own calling. We labor mainly to acquire position and comforts, but how few of us are really students and care more for the advancement of science than for our own 'getting-on' in the world.

How seldom has an American physician made independent and systematic investigation in any of the sciences connected with medicine!"

White describes in his memoirs the effects of his attack on contemporary medical education: "This address was followed by the most lively agitation in the faculty. . . . Finally the scheme of the reformers . . . was adopted (1871). . . . By this hard-fought victory the school made a nine months' course compulsory, adopted a graded curriculum extending over three years, and obliged candidates to pass a written and thorough examination in every one of the great departments of medicine." Surgeons today will forgive him for a final shot directed at the venerable Henry J. Bigelow: "My own examination in surgery at graduation was the question, 'Well, White, what would you do for a wart?'"

But Bigelow was not silenced, and rose in defense of the educational policies of the old school at the Massachusetts Medical Society.¹⁰

"It is plain," he said, "that the mass of work must be performed by the . . . practitioner, who has been educated with the view of turning his acquirements to immediate practical account, and whose business so occupies him that he contributes comparatively little to the absolute advance of knowledge. . . . You are to provide 50 such plain and competent men for one who knows more."

"These remarks are not intended as a plea for mediocrity. It should be remembered that our present system of medical education, imperfect as it may be, produces men eminent in science, and furnishes able teachers as well as distinguished practitioners. Most eminent men are in a large degree self-made, and have pursued their subject from the attraction before them, and not from a stimulus behind. The material out of which philosophers are made is largely supplied from their own intrinsic and determined will. Genius is talent with a strong driving power. . . . You cannot create this talent. . . . You may, indeed, give it opportunity, but you cannot force it."

"Whatever else it may or may not do, a medical school should aim first, then, to give a plain, sound, solid education, without error, if without ornament."

Although Bigelow was outvoted in the University, there was a redoubt to which he could retreat—the voluntary hospital, in which his word in surgery was supreme. Universities were quite remote from the voluntary hospitals of 1870 and, in fact, to this day must tread with caution within their portals.

The Voluntary Hospital,* as an institution, has fully as ancient a lineage as the University, for the germ of the hospital system existed long before the Christian era. The Greek and Roman temples resembled "clinics" more than "churches," and their priests were well versed in medicines. The history of the hospital movement is a long and romantic story; but "undoubtedly the greatest event in the history of the hospital movement throughout the world was the coming of Christ at the very moment that the Roman Empire had united all

* There have been in this country many integrations or actual mergers between voluntary hospitals and universities, and in some instances between voluntary hospitals and government, either state or municipal. Also, many large municipal and state hospitals have developed after the pattern of voluntary hospitals.

the Western nations into one vast civilization."⁵ With Christ came the concept of Charity.

This great motivating force, the desire to relieve suffering on its own merits and for its own sake, became the soul of institutions destined to evolve into the voluntary hospitals of the Western World—at the moment the iron curtain was descending along the Rhine. Professional historians must assume responsibility for tracing the evolution of these institutions through the devious pathways of the Middle Ages, the Renaissance, and the Holy Roman Empire. The fact remains that at the opening of the 19th century, medicine and medical education in Germany were found within the University and incorporated into the framework of the State. Medicine and medical science thus received a direct stimulus from university philosophic thought, and aided by the financial support of the State, entered its productive period of scientific advance.

In England and in America there had been no recognition of a duty of the nation to the sick, "except in so far as they become a danger to the community, like the ancient lepers." The care of the patient was centered in voluntary hospitals, separate from universities and outside the framework of the state. English hospitals had established their own schools of medicine, a development copied in this country but to a limited extent.

The sincerity and idealism of the Voluntary Hospital cannot be written off as self-interest and bigotry, as some have tried to do.* In 1886 Henry J. Bigelow was again voicing his wrath, but at this time against a force that was striking at the soul of his voluntary hospital. In an open letter¹¹ he warned the Trustees of the Massachusetts General Hospital that "some members of the Staff have a desire to use the institution to their professional emolument. In my opinion any such changes, however plausibly introduced, will inaugurate for the Hospital an era of decline. . . . Its Trustees should weigh carefully any measure which would tend to confuse the administration of a great public charity with the promotion of private interests."

Charity in the literal sense and in the form of alms dispensed by Lady Bountiful may disappear from the American scene, but the medical profession would do well to treasure such vestiges of it as remain. Charity in the material sense is symbolic of Charity in the broad spiritual sense—the desire to relieve suffering for its own sake. This is the compelling force of Humanism, that I have placed with Science and Technology in the basic content of Surgery. Charity in this larger sense is the most precious possession of Medicine. As motivation for the physician, it has been closely entwined with teaching and research. It is expressed in his basic rules of ethics and determines the privileges and trusted position of the physician in the social order. The foundations of the Voluntary Hospital rest upon this great concept of Charity; it is found in the blood and sinews of these institutions today. It is without exact coun-

* "Conservatism, vested interests, absence of true university ideals, lack of resources, lack of leadership and excessive dependence on tedious committee procedure." "Staffs, huge, unorganized, unpaid, unassisted, had been put in charge; appointments went variously—by political pull, by personal favor, occasionally even by merit."⁷

terpart in the traditions of the University; it is far too intangible to be codified by the State.

I have tried to show that up to 1870 medicine and surgery in the Graeco-Roman-Franco-British-American stream were pursuing a steady but slow evolutionary trend. "There was no sharp line between the practising and the teaching profession. The practitioner taught—and, if he pleased, investigated." From this stream even then was emerging Lister and, before him, Claude Bernard, Louis, Bright, Laënnec, Charles Bell, Jenner, the Hunters, Sydenham, and William Harvey. Flexner, in referring to leaders of this type, states that "their situation and environment instead of helping, progressively impeded them." It would be of more interest to learn what happy combination of circumstances led to their appearance.* By 1870 floods of specialized knowledge and technics were bursting forth from German and Austrian universities. The proposal of the youthful President Eliot to change medical education was supported by the members of his faculty who sensed the situation. Although the position of the preclinical departments of the Medical School was strengthened and the curriculum graded and extended, what might have been a major effect upon medical education was attenuated by the fact that clinical teaching was centered in voluntary and municipal hospitals, outside direct university control. No thought whatsoever was given to the postgraduate period of surgical education; that remained unorganized at the apprentice and private assistant level.

The story of the opening of the Johns Hopkins Medical School (1893) is known to all students of medicine. But here I shall narrow the focus to surgical education at the postgraduate level. In designing the surgical clinic at the Hopkins, Halsted duplicated in so far as possible the pattern of the German clinics. "It was our intention," he stated, "originally to adopt as closely as feasible the German plan, which, in the main, is the same for all the principal clinics of the German universities. The house surgeon, or first assistant, as he is called in Germany, is selected, after several years of service, from a number of well-tried assistants. There is no regular advancement from the bottom to the top of the staff of resident assistants. Only a small proportion of these venture to entertain the hope of becoming first assistant. Occasionally an assistant from another clinic may immediately, or almost at once after transfer, succeed to this position over the heads of those who have served many years. This admirable system, which undoubtedly has

* In his President's Address, American Society for Clinical Investigation, May 2, 1927,¹⁴ Eugene DuBois gave a critical and pessimistic account of the situation and environment that had been established in this country, as of that date, supposedly to nurture scholars of this stature. He posed the question of how a young Harvey or Laënnec might fare in twentieth-century university medicine. In answer to his own question, DuBois decided that these gentlemen "after a good look at the present conditions . . . would realize that they would be happier in their own small, inefficient but comfortable centuries. Harvey would beg to be returned to the England of James the First, Laënnec to the France of Louis the Eighteenth."

its disadvantages, is possible only in a country where like conditions prevail and a close affiliation exists between the universities or where some great inducement exists for the making of assistants of the highest possible order. The professor of surgery, or the surgical chief, desires to secure as his first assistant or chief of staff, a man of great promise, not only because of the obvious immediate advantage to the clinic, but because such an assistant is likely to have tendered him, ultimately, the chair of surgery in some smaller university. It is a matter of great satisfaction and pride to a professor of surgery to have supplied from his staff one or more university chairs. . . ."¹²

The new experiment at the Hopkins was eminently successful. Halsted himself was a thoughtful and productive scholar. There was gold to be extracted from the medical sciences that fringed on surgery, and their technics of anatomic dissection, histopathology, and taxonomic bacteriology were readily acquired. Surgical Technology was being developed and modified at a rapid pace in full exploitation of the discovery of antiseptics by Lister. Halsted's hope that his able pupils would be called to chairs of surgery elsewhere in the country was fulfilled.

With an energy and enthusiasm typical of America, the experiment, started on a modest scale in Baltimore, was soon repeated throughout the country. New university clinics were created on the strict organizational pattern described by Flexner.⁷ The blueprints were drawn in detail and the specifications written with precision. Nothing was left to a "gentlemen's agreement." The full-time system in clinical surgery was to "abridge the evolutionary process by setting up summarily the conditions necessary to scientific development on the clinical side."

There can be no doubt that the remodeling of American surgery was badly needed; there is no doubt that it came at a critical time. It helped close the gap between the discoveries of the laboratories of medical science and the clinics, as it was designed to do; it came at a time when the elaboration of surgical technics had opened the field for a gold rush in the pursuit of surgery as a trade. Successful practitioners scrambling for the prestige of a professorship all too frequently were preoccupied with large practices and with tastes similar to those of their friends and patients—the "robber barons" of commerce and industry. The public charity of the days of Henry J. Bigelow came to be referred to as "exploitation of the profession."

But the assumptions and conditions underlying the introduction of the full-time system as an attempt to quicken evolutionary processes, must clearly be recognized. The rapid expansion of the university hospital system called for a considerable number of physicians and surgeons to fill important posts. Flexner mentions this problem: "Will medicine," he asks, "enlist in its service as devoted, enthusiastic, and self-forgetful workers as have been absolutely essential to the development of other sciences? Or will physicians and surgeons crave conditions that the university cannot create or maintain?"

What kind of men were these German professors that it was sought to emulate? J. C. White described them. He tells us that "in Germany the

celebrated physician first makes for himself a name of incessant toil and self-sacrifice. He cares neither for society, for appearances, for comfort, only for science." Even more vivid is his description of an individual: "Oppolzer comes in punctually. I cannot give my first impression of him. It was, perhaps, that his pictures belie him, that he had made a very hasty toilette, had forgotten his collar, and had not made the same use of the Danube as we do of the Cochituate. . . . We may pardon the want of neatness, when we consider the low rank in social life to which scientific men of Austria are condemned."

That the organizational pattern be considered all-important is a familiar American tendency. Here even Flexner had reservations: "A full-time organization will not transform a sterile clinician into a proper university professor . . . it will not produce ability and enthusiasm where they do not exist; it will not make the sterile clinician fertile." There is evidence that Halsted fell into this trap. "Why," he asks, "was Germany the country first to adopt antiseptic surgery? Why did almost every surgeon in every German university eagerly embrace Lister's system almost at the same moment? . . . The answers to these questions are, I believe, to be sought mainly in the character of the scientific training of surgeons in Germany. . . ." Therefore he set up an identical training schedule. Wouldn't it have been more pertinent to have asked: Why did Mr. Lister, FRCS, Eng. and Edin., who commenced a course of Lectures on the Principles and Practise of Surgery on November 7, 1855, and helped Mr. Syme in his consulting rooms on Rutland Street—why did this Mr. Lister *discover* antiseptic surgery?

It may be noted also that the organizational pattern chosen for transplantation had already started to deteriorate. Flexner admits that "in Germany during the last 30 years, despite the firm academic anchorage on which I have dwelt, the successful professor of the clinical subjects has time and again drifted away from his clinic and his laboratory. In recent years many university professors have established private clinics, managed as business enterprises. . . . Thus the professional preoccupations of clinicians make sad havoc with professorial duties." This has a strangely familiar sound today.

In 1947 we have a larger perspective of the structure of German medicine than was given to those who so enthusiastically brought its pattern home to our shores. The last twenty years have shown how fragile was its bloom and how shallow were its roots. German medicine went down with the state through degradation to destruction. It has been profoundly disturbing to think that the medical profession, as individuals, shares the responsibility and to learn that in some instances individuals actually participated in the conspiracy.¹³ Medicine was powerless to act in behalf of the humanity it should have been serving or to raise its voice to check the downward trend. The same was true of the Universities. In the shameful history of the Nazi conspiracy there was no happening more tragic than the failure of the Universities and of University Medicine to utter a word of protest. Was it solely because of their position within the framework of the state? Or had Medicine, neither pure

Science on the one hand, nor pure Humanism on the other, made itself vulnerable in Germany by neglecting Humanism in the pursuit of Science? Science is but one of the four components in the Content of Medicine.

There are, of course, many secondary forces in this troubled stream of Surgery that have created their own whirlpools and eddies. These may be external, shaped by the social order, or internal, derived from Surgery itself. An example of the former is the complex structure of medical economics within which surgery is regarded as a trade. I have shown how the trade interest of surgery appears and reappears in relation to teaching, research, and the care of the patient. It has been encountered in the Hospital and in the University. It is a dominant factor in problems now vital to the State, such as the maldistribution of specialists and the spiraling cost of illness.

The trade interest of surgery now has relatively little influence on undergraduate medical education, for this is sheltered under the wing of the University. It is definitely shaping graduate education, so important in the training of the surgeon. The spread of "Halsted's resident system," established to further science and education in surgery, has found great impetus in the need of present-day hospitals and clinics for many young and willing pairs of hands. Exploitation of these hands by neglect of the minds and ideals that must be developed to guide them will repeat the evils of the undergraduate proprietary schools of the last century, when "the teaching of medicine was, directly, in cash, and indirectly, in prestige, a profitable business."

With better basic education, it should be found possible to shorten, rather than necessary to lengthen, special technical training.* The dangerous gospels of force and uniformity are being spread in this critical area of adult education in support of organizational patterns originally conceived as aids to science and teaching, but developed in many instances as "training without a well-conceived educational plan." The time may not be distant when government will wish to take a hand and freeze in compulsory law the structures of graduate training that are being erected. It would be unfortunate were this to happen before these structures have been tested by further experience. In fact, this period of adult education is far better left entirely outside the law. But it would be well to remember that the interval between the reform in undergraduate education and the incorporation of the reform into law by the state was brief. It is but a short step from dictatorial certifying boards within the profession to proscribing boards within the law.

An example of a secondary force arising from within surgery is the fragmentation that has resulted from specialization. The origin of a specialty is usually traceable to a concentration of effort inspired by a desire to extend the scope of surgery by progress. Too often, however, a specialty has been perpetuated as a watertight compartment with emphasis on the mystic rites of technology and neglect of further progress; and ultimately there appears an unmistakable intrusion of the interests of the trade.

* Wartime experience has shown in many fields that it is possible to train men faster than had been supposed.

This brief foray into medical history has shown the need for new soundings in the onrushing stream of Surgery. On the one hand, it is time to face facts and agree that increased emphasis upon Science has resulted in progress that has guided Surgery out of medievalism and established the benefit of its skills as one of the rights of humanity. No longer could a Henry VIII or any other ruler close the hospitals of a great nation. It is also evident that the "reforms" of the last 70 years came at a critical time when the self-interest of surgery as a trade, armed by a great expansion of Technology, might have been a real threat to the functions of teaching and progress.

On the other hand, the opposition to the reforms that were introduced brought forth criticisms that were not entirely expressions of unenlightened self-interest, despite the fact that many local episodes of bitterness and conflict are traceable to encroachment on the monopoly interests of trade. There was something deeper—an inarticulate and sincere concern lest the dazzling light emanating from Science eclipse that other content of Surgery I have called Humanism. The humblest member of the profession is vested with the right and the duty to enter his protest against such a threat, for the obligation written into the Hippocratic Oath makes every practitioner of the Art share responsibility for Teaching: "I will impart this Art by precept, by lecture, and by every mode of teaching." This is an obligation unique to our profession.* While teaching in the literal sense may be delegated to a limited group, responsibility for the preservation of balance in the Content of Medicine rests on the profession as a whole, and not on some chosen segment that might veer like a weathercock with every change of wind or on some other occasion remain fixed long after the prevailing wind has changed.

Surgeons are men of practical affairs and tend to be self-conscious about a direct expression of the ideals upon which their profession rests. But what I have said has been said many times before. It is found in the writings that inspired and guided the growth of the Voluntary Hospital. It is found in the essence of what is called Western Civilization. It was set down long ago in very simple words: "And though I have the gift of prophecy and understand all mysteries, and all knowledge; and though I have all faith, so that I could remove mountains, and have not charity, I am nothing."

This, I believe, is the real warning Medicine gave to those enraptured by German Science. Medicine is too close to the needs of humanity, and is too loyal a friend of mankind in times of fear and trouble, to cast aside abruptly its heritage of Christian ethics for what has been called the "moral irresponsibility" of Science. The future of Medicine and very possibly the future of Science itself will be determined by the wisdom and kindness with which the great gifts of Science are assimilated and made available to human needs. "I do not know," writes George Sarton, "who is the poorer:

* Truly great teachers of mankind have expressed little concern about who should carry forward their precepts. Just as Hippocrates spread the responsibility for teaching to all of his disciples, so did Christ. Later the successions of Professors and Popes appeared with delegated responsibilities for the perpetuation of organized experience (and dogma).

the old humanist without understanding of science, or the scientist . . . without reverence. I do not know which is worse: idealism without knowledge, or knowledge without idealism. We need both equally in order to go forward and prepare the dawn of a new age. . . ."¹⁵

There can be little doubt that Surgery is facing further change in the relative emphasis placed on the component parts of its content. Science will increase, and scientifically based Technology will slowly replace Empiricism. There are certain to be changes in the organizational patterns formed by Hospital, University, and State. These changes may be brought about by explosive forces in the restless external social order, or anticipated by a sensitive government. Change is to be feared only if those responsible for the preservation of essential values falter in their task. In fact, change is welcomed in so far as it may strengthen the profession to meet the new challenges that confront our civilization.

In times of change there is need for wisdom both in the external social order and within the profession. Spokesmen who loudly proclaim measures based on self-interest will not be tolerated. A hold-fast in Science is essential, but this represents only a part of the strength of Surgery. By maintaining the ancient bond with humanity itself through Charity—the desire to relieve suffering for its own sake—Surgery need not fear change if civilization itself survives.

REFERENCES

- ¹ Allen, Phyllis: Medical Education in 17th Century England. *Jour. History of Medicine*, 1, 115, 1946.
- ² Oxford University Statutes (as abstracted and quoted by Allen).
- ³ Ward, John: Diary of the Rev. John Ward. Charles Severn, London (1839). Quoted by Allen (p. 127).
- ⁴ Needham, Marchmont: *Medela Medicinæ*, a Plea for the Free Profession of the Art of Physick. . . . London (1665). Quoted by Allen.
- ⁵ Evans, A. Delbert, and L. G. Redmond Howard: *The Romance of the British Voluntary Hospital Movement*. London, Hutchinson and Co., Ltd.
- ⁶ Mumford, James G.: *The Quarterly of the Harvard Medical Alumni Assn.*, April, 1902.
- ⁷ Flexner, Abraham: *Medical Education—A Comparative Study*. New York, The Macmillan Co.
- ⁸ Croce, Benedetto: *Germany and Europe*. Random House, New York (1944).
- ⁹ White, James C.: *Sketches from My Life*. Riverside Press, Cambridge (1914).
- ¹⁰ Bigelow, Henry J.: *Surgical Anaesthesia. Addresses and Other Papers*. Boston, Little, Brown and Co.
- ¹¹ Bigelow, Henry J.: Letter dated Feb. 18, 1886; printed but not published. Also: *Fees in Hospitals*. Boston Med. and Surg. Jour., April 18, 1869.
- ¹² Halsted, William Stewart: *The Training of the Surgeon. The Annual Address in Medicine, delivered at Yale University, New Haven, Conn., June 27, 1904. Surgical Papers, by The Johns Hopkins Press, Baltimore (1924). Vol. II, 512 (reprinted).*
- ¹³ Affidavit (G) of Fritz Ernst Fischer, 21 November, 1945. *Nazi Conspiracy and Aggression*, Vol. VIII: 635. U. S. Government Printing Office, Washington (1946).
- ¹⁴ *Science*, LXV: 587, June 17, 1927.
- ¹⁵ Sarton, George: *The History of Science and the New Humanism*. Harvard University Press, Cambridge (1937).

GASTRO-ESOPHAGEAL RESECTION AND TOTAL GASTRECTOMY IN THE TREATMENT OF BLEEDING VARICOSE VEINS IN BANTI'S SYNDROME*

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OF THE VARIOUS OPERATIVE procedures that have been used for esophago-gastric hemorrhage in Banti's syndrome, splenectomy, porta-caval shunt and injection of the esophageal varices with sclerosing solutions are the only ones of much value.

Splenectomy^{1, 2} has given its best results in the uncommon cases with blockage of the splenic vein. When extrahepatic obstruction of the portal vein is present, splenectomy, by removal of a large area of the portal bed, may ameliorate the hemorrhage for a variable length of time, but it usually recurs as the hypertension is built up again. Porto-caval shunt^{3, 4, 5} introduced by Whipple and co-workers is the ideal treatment, since in addition to reducing the elevated pressure and tendency to hemorrhage of the gastro-esophageal varices, it relieves the passive congestion of all structures drained by the portal system. But in some cases of fibrous or cavernomatous transformation of the portal vein, it has been impossible to anastomose either the main trunk or one of its large tributaries with the inferior vena cava even when a vein graft was utilized. Also when anastomosis was possible, the communication has sometimes narrowed or closed. Previous splenectomy precludes splenorenal anastomosis. After successful anastomosis, there is still the possibility of hemorrhage from the already established gastro-esophageal varices.

In certain hands^{6, 7} the injection of esophageal varices with a sclerosing agent has frequently controlled esophageal hemorrhage for worth-while periods of time. Moersch⁸ of the Mayo Clinic has recently made a follow-up study of 22 cases for periods of three or more years after injection. Twelve have had no more bleeding, four are living with continued hemorrhages, three are dead of hemorrhages, and four are dead of unknown or unrelated causes.

An additional measure to be considered when these techniques either have failed or for emergent or other reasons cannot be applied, is resection of the bleeding segment. This is especially true since the recent mortality for both transthoracic esophago-gastric resection⁹ and total gastrectomy^{10, 11} for carcinoma in experienced hands is under 15 per cent and after either operation at least a fair state of health may be maintained for an indefinite period. The first reported case of one-stage, transthoracic esophago-gastric resection, performed by Adams and Phemister,¹² is alive and well nine years after operation and patients have lived for years after total gastrectomy with only mild anemia and slight impairment of nutrition.

Two patients with Banti's syndrome have been treated, one by total gastrectomy and one by transthoracic esophago-gastric resection. In each case

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the hemorrhages began at an early age and persisted after splenectomy, the liver was normal and the general health was little impaired except by the bouts of bleeding.

CASE REPORTS

Case 1.—C. C., male, age 18 years, was admitted to the hospital 7-7-44 with the chief complaint of hemorrhages from the gastro-intestinal tract beginning at the age of six. Since the age of four his general health had been below par and he had had periodic attacks of malaise, weakness and fever. At the age of five an enlarged spleen was noted and since the age of six he had had repeated bouts of hematemesis and melena which were often associated with febrile attacks. At the age of ten he entered the Children's Memorial Hospital, Chicago, where he was found to have a markedly enlarged spleen and blood examination revealed R.B.C. 395,000, Hb 70 per cent, platelets 6800, W.B.C. 3000, Diff. Polym. 63, L. 32, M. 4, E. 1, Ret. 3 per cent, coag. t. 3 min., B.t. 4 min.

Splenectomy was performed. The spleen weighed 325 Gm. and microscopically showed the picture characteristic of Banti's disease. Following the splenectomy he continued to have bouts of hematemesis and melena and at the age of 16 they increased in severity. Eighteen months before admission, an esophagoscopy examination elsewhere revealed extensive varices of the lower and middle portions of the esophagus. Injections of the varices with a sclerosing solution were made on eleven occasions at that time, on nine occasions five months later, and on five occasions seven months after that. But two to four months after each set of injections, very severe bouts of bleeding occurred calling for numerous transfusions. The only change was that after starting the injections, the blood all passed by rectum, whereas before it has passed both by mouth and by rectum.

On admission, two months after the last hemorrhage, he felt well except for moderate weakness. Physical examination revealed essentially normal findings aside from an old left upper paramedian laparotomy scar. There were no paraumbilical varices or hemorrhoids. The liver was not palpable and the cephalin flocculation, colloidal gold and bromsulphalein liver function tests were normal. Blood examination showed R.B.C. 5,100,000, W.B.C. 8,900 and Hb 14 Gm. per cent. On esophagoscopy examination the lining of the middle and lower esophagus was thickened from the previous injections and few varices were seen. Roentgenologically, when the Valsalva test was applied, the esophagus showed some irregularity of the barium shadow and the proximal stomach showed filling defects which were interpreted as due to varices. The stomach was manipulated under the fluoroscope and the patient soon presented symptoms of hemorrhage which became severe. Bleeding continued irregularly for 20 days, and necessitated 24 blood transfusions.

The diagnosis was made of bleeding gastric varices and a total gastrectomy decided upon. Severe bleeding started again on the early morning of the day for which the operation was scheduled. Rather than risk the chances of another severe bout of bleeding, an emergency laparotomy was performed. The stomach contained a large amount of blood and the coronary vein and branches to the lesser curvature were enlarged. There was blood in both small and large intestines and no sign of enlargements of the branches of the superior mesenteric vein. The liver was of normal appearance. Total gastrectomy, esophago-jejunostomy and jejunostomy were performed. Bleeding continued during the operation and 3500 cc. of partly clotted blood was found in the excised stomach. Thirty-one hundred cc. of blood was transfused during and shortly after operation. The postoperative course was relatively uneventful.

Pathology.—Externally the stomach looked normal aside from the moderately dilated veins on the lesser curvature. The gastric mucosa had normal folds and was of normal color except for a few petechiae. No ulcer or definite point of bleeding was found.

Microscopically, the outstanding feature in sections from all parts of the stomach

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was the large size of submucosal veins and mucosal venules. Especially large, empty, submucosal veins were found near the lesser curvature, close to the cardia (Fig. 1). Some of them had thin walls, with plaques which appeared to have been formed from organized mural thrombi. No fresh thrombi or open vessels were observed, here or

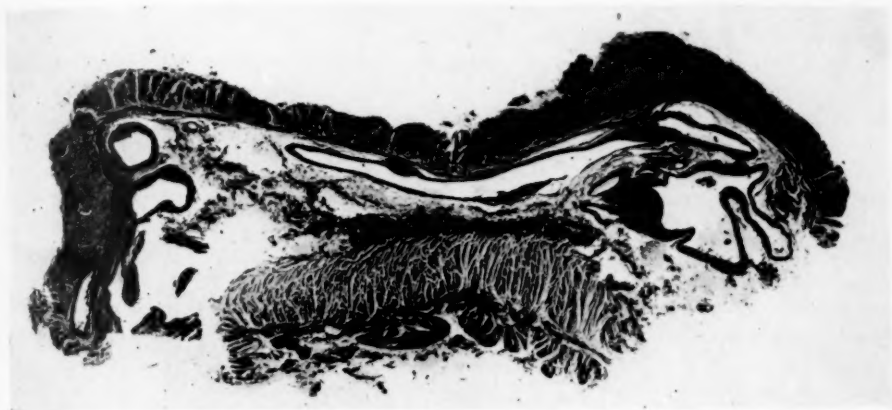


FIG. 1.—Case 1: Collapsed submucous gastric varices near the cardia. ($\times 9$)

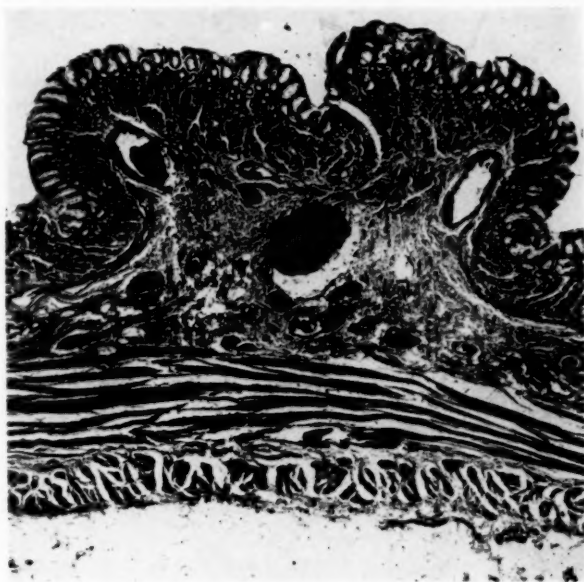


FIG. 2.—Case 1: Dilated veins in the wall of the fundus.
($\times 27$)

elsewhere. The loose structure of the connective tissue adjoining the veins was probably an artifact. In the distended state the flat collapsed vein of Figure 1 must have caused the mucosa to bulge, and may have impinged on the dense fibrous tissue close to the muscular coats.

Many of the rugae contained numerous submucosal veins, sometimes as in the fundic

fold illustrated in Figure 2, stimulating an angioma. The two large veins in this fold protruded through the muscularis mucosae. Often connections could be traced between mucosal and submucosal veins. Such a channel in the mid-gastric region (Fig. 3) drained the basal venous plexus of the mucous membrane, and the numerous venules and capillaries between the gastric glands. It was sometimes possible to trace serially one of the large straight venules from a channel communicating with a large submucosal vein almost

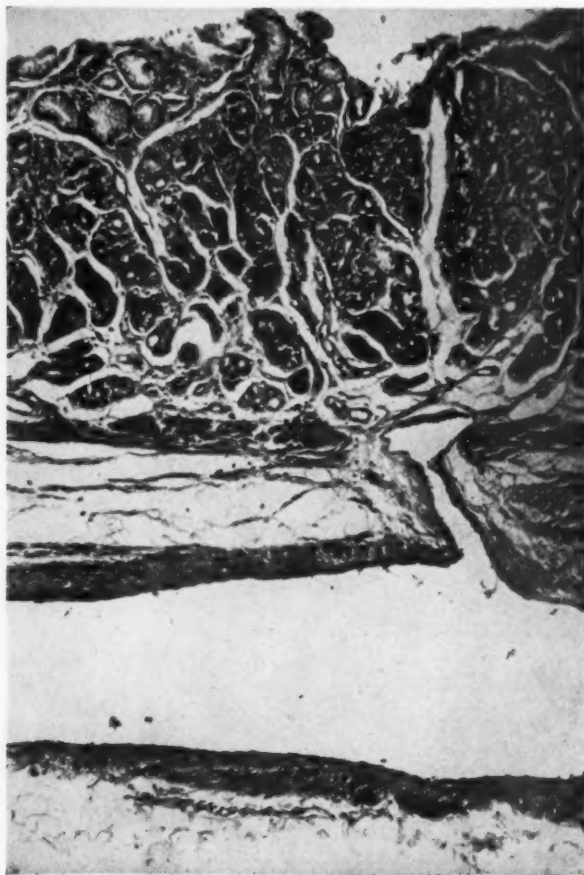


FIG. 3.—Case 1: Mucosal venocapillary network communicating with large submucosal gastric vein. Mid-gastric region. ($\times 125$)

to the mucosal surface. At no point, however, was there a continuous demonstrable passage leading to the lumen. However, it is easily understood that bleeding might occur from minute surface erosions opening the tips of such vessels which would escape detection.

Even in the antrum and close to the pylorus venous distention and mucosal changes were evident, though nowhere so marked as near the cardia. Hemorrhage about a large pyloric vein as it passed through the muscle coats was probably the result of operative trauma. The largest external veins were close to the cardia. These coronary veins were not thrombosed, and were remarkable only because they were sclerotic, with walls thicker than those of the arteries they accompanied.

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During the two and two-thirds years since operation, the patient has been in fairly good health aside from two bleeding spells, one moderate two years ago, and the other slight eight months ago. He has received injections of liver extract once a week and on 2-5-47, a blood examination revealed R.B.C. 4,320,000, W.B.C. 6,900 and Hb 13.6 Gm. per cent. Two years after operation, esophagoscopy revealed sclerosed bluish ridges in the lower esophagus but no definite varices were identified by needling and aspiration. This finding spoke against the reestablishment of important venous connections across the line of esophago-jejunal anastomosis. However, there was hematemesis at the time of the last bleeding, indicating that the blood came from esophageal varices.

Case 2.—E. K., a female age 21 years, was last admitted three and two-thirds months ago because of melena and other symptoms of hemorrhage of five hours' duration. She first entered the hospital at the age of nine years with a history of occasional bouts of hematemesis and melena since the age of four, some of which had been severe and associated with febrile reactions. Two days previously she became ill with a fever and on admission the temperature was 39°C. The only other positive finding on physical examination was a moderately enlarged palpable spleen. The initial blood examination revealed R.B.C. 4,960,000, Hb 96 per cent, W.B.C. 12,050. Ten hours after admission bleeding started with hematemesis, and marked signs of blood loss and melena followed. Six days later she was afebrile, the bleeding had stopped and the blood examination revealed R.B.C. 2,720,000, Hb 6.5 Gm. per cent, W.B.C. 4,700, coagulation time three minutes, bleeding time five minutes, platelets 260,000. Esophagoscopy revealed varices in the lower esophagus. A diagnosis was made of Banti's disease with bleeding esophageal varices.

Splenectomy was performed three weeks after admission when the patient had sufficiently recovered. The liver appeared to be essentially normal. The spleen weighed 167 Gm. and was normal in contour. Microscopically, there were the changes of congestive splenomegaly with early stages of Banti's fibroadenoma. A hyaline thrombus was found in a small branch of the splenic vein near the hilum.

The postoperative course was uneventful. Blood examination six weeks after operation revealed R.B.C. 4,370,000, Hb 74 per cent, W.B.C. 9,150, platelets 828,000. Six months later the platelets were 215,000. At widely varying intervals, since the splenectomy the patient has had bleeding spells often associated with fever because of which she was repeatedly admitted for treatment. Otherwise she has been in good general health.

Five hours before the last admission, she developed weakness and faintness and soon passed a large amount of blood by rectum. Her condition grew worse and on admission she was in marked shock from hemorrhage. Blood examination revealed R.B.C. 2,110,000, Hb 9 Gm. and W.B.C. 15,600, Prothrombin 95 per cent. Unconsciousness set in shortly before transfusion was started but she responded well to the continuous administration of 500 cc. of plasma and 1500 cc. of blood, followed by 2500 cc. of blood in the course of the succeeding five days. The hemorrhage stopped and by the 8th day she was in good general condition. Roentgenography revealed varices in the lower esophagus (Fig. 4) which were verified by esophagogoscopy.

In view of the nearly fatal outcome, the patient readily consented to operation. By a left thoracic approach through the bed of the resected 8th rib, the lower esophagus was exposed. No enlargement was noted in the veins about it. The diaphragm was opened and the liver found to be normal in appearance. The veins of the stomach were not remarkable although it was not easy to judge those of the lesser curvature. Resection of the lower three and one-half inches of the esophagus and upper two inches of the stomach followed by esophago-gastrostomy was performed. The postoperative course was uneventful, there has since been no return of bleeding and she is now in good general health.

Pathology.—The mucosal surfaces of the resected segment are demonstrated in Figure 5. A few stringy brown clots adhered to the gastric mucosa which was grossly intact. Despite the previous oozing of much blood from the cut margins, tortuous submucosal

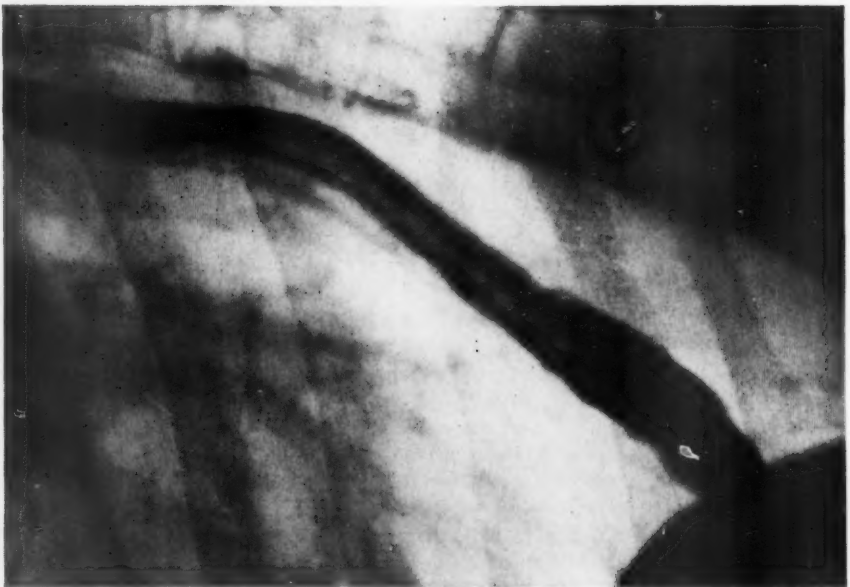


FIG. 4.—Case 2: Roentgenogram showing esophageal varices.



FIG. 5.—Case 2: Resected portions of esophagus and stomach; varices more extensive in esophagus than in stomach.

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veins were still conspicuous in both esophagus and stomach, but especially in the longitudinal folds of the esophagus. No gross defect in the esophageal epithelium could be demonstrated.

Microscopically, the largest esophageal veins were found to run in the submucosal tunic (Fig. 6). They impinged on and deformed the muscularis mucosae, and occasionally broke its continuity. Numerous collapsed smaller veins ran in the thickened mucosa, where occasionally one reached the proportions of the submucosal veins. As in the large

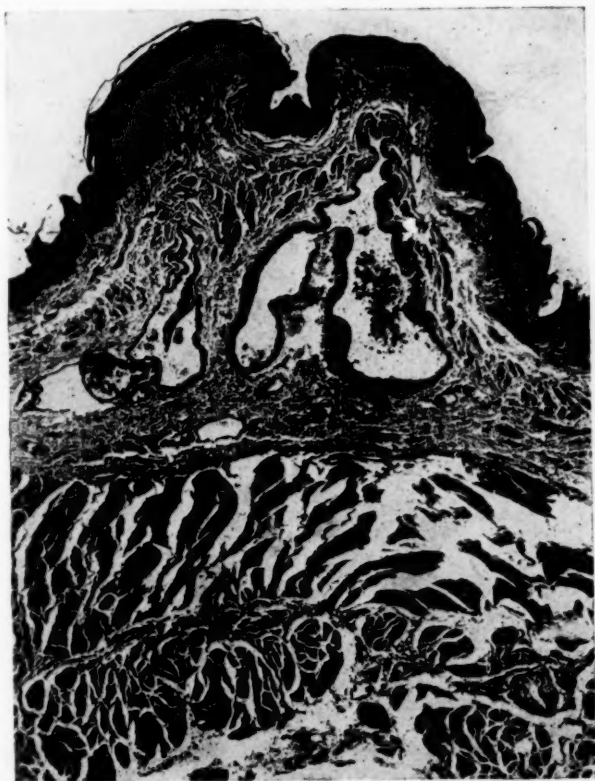


FIG. 6.—Case 2: Esophageal varices. ($\times 32$)

veins of Figure 6, the walls of the venous channels were of variable thickness. The fibrous tissue of the inner tunics was condensed, and was particularly compact close to the epithelium covering the longitudinal folds. The epithelium was thick, and on the tops of projecting folds hyperkeratotic. On the tops of projecting folds no epithelial defects were found.

Microscopically, the changes in the gastric wall were in general similar to but much less pronounced than those in Case 1. The veins in the submucosa were considerably smaller than those in the esophagus but they were much more numerous than was apparent on gross inspection. The cross-section of a ruga close to the cardia, illustrated in Figure 7, demonstrates numerous wide veins. As in Figure 2 of Case 1, large veins impinged on the mucous membrane, and lay within or above the muscularis mucosae. Figure 8 illustrates in detail one of these veins lying in the basal portion of the mucosal venous plexus. The thickest part of its wall represents an organized mural thrombus. Its

large branch in the mucosa above is surrounded by dense fibrous tissue, representing an organized thrombotic vein. The artificially loose structure and distortion of the mucosa illustrated here was repeated in other sections which included large veins and wide venules. In some rugae the glandular pattern was even more distorted, resembling the changes illustrated in Figure 3 of Case 1. No erosions nor points of recent bleeding were identified.

No grossly visible defects to account for the recent hemorrhages were found in either resected specimen. The conclusion based on clinical facts that the stomach was the important source of bleeding prior to the gastrectomy in the first case was supported by

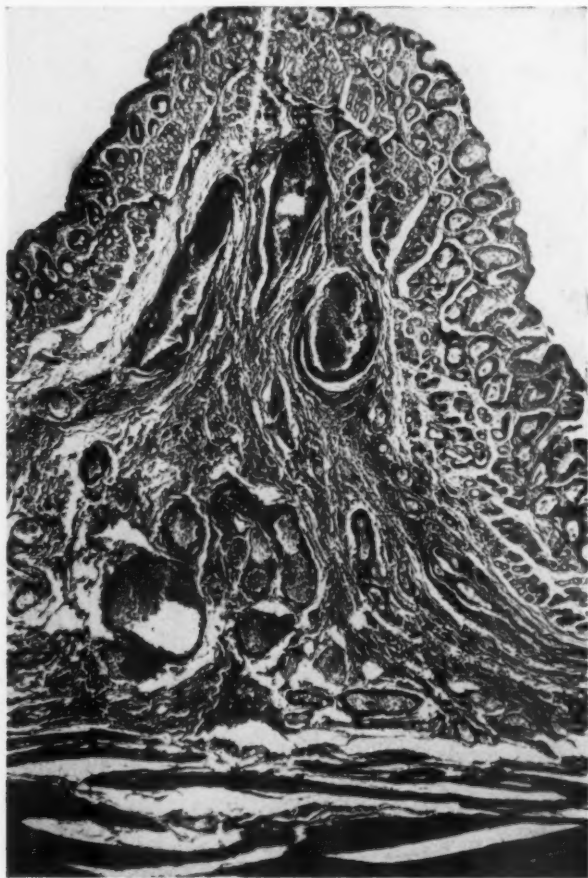


FIG. 7.—Case 2: Large veins in a gastric ruga. ($\times 60$)

histologic studies. Bleeding from the stomach as well as from the esophagus probably had occurred in the second case, judging from the presence of thrombosis in branches of the mucosa. Under some conditions, the gastric component of gastroesophageal varices may provide a greater danger of hemorrhage than the esophageal component.

DISCUSSION

The term "gastro-esophageal" fittingly characterizes the varices associated with chronic hypertension in the portal, gastric and splenic veins. Dilated gastric veins were demonstrated in both cases here reported. Especially in

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Case 1, where sclerosing injections had obliterated many of the esophageal varices, gastric veins were everywhere enlarged, particularly so near the cardia. In Case 2, with patent esophageal varices, venous dilatation was similar but less marked. Clinical and anatomical evidence of recent severe gastric hemorrhage was present in Case 1, without grossly visible defects in



FIG. 8.—Case 2: Large vein lying internal to the gastric muscularis mucosae.

the gastric mucous membranes. The fact that bleeding may occur without gross erosions explains the frequent lack of emphasis on gastric hemorrhage associated with gastroesophageal varices.^{13, 14} The probable sources of the blood lost from the stomach without demonstrable lesion are numerous tiny ruptures through veno-capillary stomata, with the loss of too few epithelial cells to be appreciated grossly. In the average case of cirrhosis, or of Banti's syndrome, the esophageal varices are probably the source of most of the severe and sudden hemorrhages. However, these cases demonstrate how gastric bleeding may be added to esophageal bleeding, or as in Case 1, may replace it in importance.

The time has not arrived for a final evaluation of all of the various operative procedures for the control of hemorrhage in Banti's syndrome due to extrahepatic portal block. Resection of the bleeding segment like obliteration of the esophageal varices by injection, throws more load on the remaining routes of collateral circulation; but this may be justifiable because they either do not bleed at all or bleed infrequently; and if patients with extrahepatic portal block and portal hypertension especially the splenectomized ones, do not bleed to death, they may live indefinitely in good health except at the time of the bleeding bouts. Transthoracic esophagogastric resection gets rid of that portion of the varicose segment which is the usual seat of major hemorrhage, divides the vessels of the lesser curvature and of a variable part of the greater curvature, thereby reducing gastric blood supply and establishes more or less of a permanent barrier in the esophagogastric venous collaterals at the line of anastomosis. Total gastrectomy gets rid of the bleeding points when the hemorrhage is predominantly from the stomach and establishes a connection between the esophagus and jejunum which is free of varices.

Theoretically and from the meager information furnished by these two cases, resection would appear to be worthy of a trial when control of hemorrhage is impossible by means of splenectomy, porta-caval shunt and injections. Whether in threatening and emergent cases such as these two, the percentage of failures with porta-caval shunt and injections may be great enough to warrant the use of resection in advance of one or both of those procedures, remains to be determined. Splenectomy might be combined either with transthoracic esophagogastric resection, or in case of gastric bleeding, with total gastrectomy, if on exploration it is found impossible to perform a porta-caval shunt. Since wider resections than were practiced here are possible, they might be called for in selected cases.

SUMMARY

A patient with Banti's syndrome and a normal liver had frequent severe hemorrhages from gastric varices after splenectomy and extensive obliteration of esophageal varices by injections had been carried out. Total gastrectomy was performed two years and eight months ago, since which time there have been only two bleeding spells from remnants of the esophageal varices, one moderate and the other slight.

A second patient with Banti's syndrome and a normal liver was subject to severe hemorrhages which continued after splenectomy. Transthoracic esophagogastric resection was performed and varices were found in the resected segment, greater in the esophagus than in the stomach. There was no further bleeding three and one-half months after operation.

The importance of gastric varices as a source of hemorrhage is discussed.

BIBLIOGRAPHY

- ¹ Rousselot, L. M.: The Role of Congestion (Portal Hypertension) In So-Called Banti's Syndrome: A clinical and pathological study of 31 cases with late results from splenectomy. *J. A. M. A.*, 107, 178, 1937.

BANTI'S SYNDROME

- ² Barg, E. H., and J. W. Dulin: Splenectomy in the Treatment of Banti's Syndrome. *Arch. of Surg.*, **41**, 91, 1940.
- ³ Whipple, A. O.: The Problem of Hypertension in Relation to the Hepatosplenopathies. *ANNALS OF SURGERY*, **122**, 449, 1945.
- ⁴ Blakemore, A. H., and J. W. Lord: The Technique of Using Vitallium Tubes in Establishing Portocaval Shunts for Portal Hypertension. *ANNALS OF SURGERY*, **122**, 476, 1945.
- ⁵ Blalock, Alfred: The Use of Shunt by Pass Operation in the Treatment of Certain Circulatory Disorders, Including Portal Hypertension and Pulmonary Stenosis. *ANNALS OF SURGERY*, **125**, 129, 1947.
- ⁶ Crafoord, Clarence, and Paul Frenckner: New Treatment of Varicose Veins of the Esophagus. *Acta Otolaryngologica*, **27**, 422, 1939.
- ⁷ Walters, W., H. J., Moersch, and D. A. McKimon: Bleeding Esophageal Varices; Evolution of Methods Directed Toward Their Control, especially by direct injection of sclerosing solution. *Arch. of Surg.*, **41**, 91, 1940.
- ⁸ Moersch, H. J.: Personal Communication.
- ⁹ Clagett, O. T.: Transthoracic Resection of Lesions of the Lower Portion of the Esophagus and the Cardia of the Stomach. *Proceedings of Staff. Mayo Clinic*, **20**, 506, Dec. 26, 1945.
- ¹⁰ Jones, T. E., and R. W. Kehm: Total Gastrectomy; Report of 8 Cases.
- ¹¹ Longmire, W. P.: Total Gastrectomy for Carcinoma of the Stomach. *Surg. Gyn. & Ob.*, **84**, 21, 1947.
- ¹² Adams, W. E., and D. B. Phemister: Carcinoma of Lower Thoracic Esophagus: Report of Successful Resection and Esophagogastrostomy. *Jour. of Thor. Surg.*, **7**, 621, 1938.
- ¹³ Moschowitz, A. V.: Massive Hemorrhages from the Stomach Without Demonstrable Ulcer. *Am. J. Med. Sci.*, **152**, 714, 1915.
- ¹⁴ Bortz, E. L.: Diffuse Hemorrhage from the Stomach. *Arch. Int. Med.*, **50**, 1, 1932.

DISCUSSION.—DR. ALFRED BLALOCK, Baltimore, Md.: Approximately two years ago I operated upon a 39-year-old woman who had bleeding esophageal varices with the intention of carrying out a procedure such as Doctor Phemister and Doctor Humphreys have described. On opening the left lower pleural cavity many varices could be seen on the outside of the esophagus. Two large plexuses of such vessels were removed (lantern slide showing dilated veins). We performed this operation rather than that of removal of the lower part of the esophagus because it appeared to be a less dangerous one. However, the bleeding continued and I wished subsequently that I had carried out the procedure described by Doctor Phemister.

Fortunately this patient had not had her spleen removed and in that respect she presented a problem somewhat different from that of the patients described by Doctor Phemister. Since the bleeding continued, we decided to perform a renal splenic vein anastomosis as developed and popularized by Dr. Arthur Blakemore and Dr. Allen Whipple.

(Motion picture showing renal splenic anastomosis.) The incision was performed through a left transverse abdominal incision. Other methods of approach have been recommended. For example, Doctor Linton of Boston uses a left transpleural approach. The spleen was used, exercising great care not to injure the splenic vein. The kidney was delivered into the incision. The renal artery was occluded temporarily. The renal vein was occluded proximally and distally with rubber shod clamps and a transverse opening was made into the vein between the points of occlusion. An end-to-side anastomosis was then performed between the proximal end of the splenic vein and the side of the left renal vein. The intima was approximated and everted by the use of 00000 silk on an atraumatic needle. By the use of the end-to-side anastomosis, it is not necessary to sacrifice the kidney. Furthermore, the experimental observations of Dr. T. N. P. Johns

and myself indicate that an end-to-side anastomosis is more apt to remain patent than is an end-to-end anastomosis in which the kidney is removed. It seems likely that the blood returning from the kidney serves to maintain patency of the anastomosis. A better procedure is that recommended by Doctor Blakemore, in which one only partly occludes the renal vein during the time that the anastomosis is being performed. This was not possible in the present case because the renal vein was not very large.

The present patient has had no further bleeding since the operation, but the interval has been only a couple of months. However, the results in other cases upon whom Doctor Blakemore, Doctor Linton, I and others have operated with a longer time follow-up are encouraging.

Nevertheless, I must agree with Doctor Phemister that patients with bleeding esophageal and gastric varices present exceedingly difficult problems and it is quite likely that the best means of treating them has not yet been evolved. I am very much impressed by the results reported by Doctor Phemister and I think that this method will find further useful application in the treatment of bleeding varices, and particularly so in the case of those patients who have had a previous splenectomy.

DR. OWEN H. WANGENSTEEN, Minneapolis, Minn.: Doctor Phemister stressed the hydrostatic factor as the important one in bleeding from esophageal varices. There is another item which, I believe, may be equally as important, viz.; the acid-peptic digestive factor.

Bleeding from the mucosa of the lower esophagus or stomach in the presence of portal hypertension, whether occasioned by portal cirrhosis or Banti's disease, appears to be due in part to the circumstance that erosions in these areas are readily produced in the presence of portal hypertension. This evidence has been published elsewhere (Canadian Med. Assoc. J. 53, 309, 1945) and here it need only be said that portal hypertension definitely abets the ulcer diathesis. In our laboratory, histamine implanted in beeswax has proved a useful tool in exploring factors which are believed to abet the ulcer diathesis as well as in assaying the protective merits of an operation against ulcer. Whereas, a 75 per cent gastric resection performed with a short afferent duodenojejunal loop will protect dogs regularly against the histamine-in-beeswax provoked ulcer, a 90 per cent resection will not protect regularly when a simultaneous portal hypertension has been brought about (Proc. Soc. Exper. Biol. & Med. 59, 234, 1945).

The late Professor Eppinger pointed out in his monograph on liver disease that approximately 20 per cent of patients with cirrhosis die of hemorrhage. Deaths from hemorrhage and ascites in portal hypertension are owing essentially to mechanical causes—the increased venous pressure, and may precede actual hepatic insufficiency by a long interval. All operative procedures directed at correcting hemorrhage in progressive hepatic cirrhosis are essentially palliative in nature, for we do not know how to arrest failure of hepatic functions. Yet, life may be prolonged through operative procedures which lessen the tendency to hemorrhage. In the Blakemore procedure this end is achieved by diverting the blood from the portal system to one of the systemic veins. In cirrhosis such a procedure may not improve liver function and in thrombophlebitis of the portal and splenic veins (Banti's disease) the thrombus may extend and compromise the return of blood from the small intestine.

In performing total gastrectomy for bleeding esophageal varices, in addition to getting rid of the acid-peptic digestive factor, Doctor Phemister did one other important thing; he separated the esophagus completely from the higher venous pressure of the portal circulation. In the 90 to 98 per cent gastric resection which I have employed for esophageal or gastric hemorrhage occasioned by portal hypertension, this latter feature of total gastrectomy is absent, in that one or two vasa breviae still connect the submucosal lakes of the lower esophagus to the portal circulation. I am inclined to believe that a 95 to 98 per cent gastric resection or a total gastrectomy are physiologically sound in the management of esophageal varices even though they do not approach the problem as

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directly as does esophagogastric resection. Moreover, patients with bleeding from the upper reaches of the alimentary tract who have hepatic cirrhosis or Banti's syndrome appear to have generous amounts of free hydrochloric acid in their gastric juice. When on exploration, the liver appears normal as it usually does in Banti's disease, the management of the venous pressure in one of the tributaries of the portal vein is important. In thrombophlebitis of the portal vein, the venous pressure will be up, whereas in bleeding from a silent, nonpalpable gastric erosion, the venous pressure will be normal. For the latter type of case, the conventional 75 per cent gastric resection is adequate; for the portal hypertension, a 95 per cent resection should be done.

Of the three patients reported by me in 1945 who underwent extensive gastric resection for bleeding from esophageal varices, two are still alive and well. Neither has had recurrent hemorrhage. I had done earlier excisions of the spleen in both with recurrent hemorrhage. The first patient, a man who underwent ligation of the veins to the lower esophagus elsewhere, prior to submitting to a 90 per cent gastric resection at my hands, died somewhat less than a year later from complete obliteration of the portal vein. Moreover, there had been some melena prior to death. But as was related above, a 90 per cent gastric resection does not protect regularly against the histamine-provoked ulcer in the dog in the presence of portal hypertension. A few months after the extensive gastric resection, I also excised this man's right lung for carcinoma. Of the two surviving patients, one is a child with nodular hepatic cirrhosis for whom a 98 per cent gastric excision was done for repeated hemorrhages persisting ten months after splenectomy. This boy is now almost six years old and has had no recurrent hemorrhages two years after the gastric resection. The other is a young woman in her thirties with Banti's syndrome of thrombophlebitis of the portal and splenic veins. Her spleen was excised by me seven years previously with persistence of hemorrhage. There has been no recurrence of hemorrhage since the 95 per cent gastric resection done almost two years ago.

DR. J. DEJ. PEMBERTON, Rochester, Minn.: For many years I have been interested in the problem presented by Doctor Phemister; that is, the control of bleeding from esophageal and gastric varices in cases of Banti's syndrome.

In the past at the Mayo Clinic we have relied on two measures to check such bleeding, both of which are designed to reduce the hypertension of the portal circulation; namely (1) removal of the actively congested spleen in order to diminish the volume of blood entering the portal system and, (2) performance of omentopexy in order to promote the establishment of collateral circulation between the portal and caval systems. Results of such treatment as regards prevention of recurrent bleeding may be summarized briefly. Of the 173 patients who had hemorrhage before operation, 93, or 54 per cent, have had recurrent bleeding after operation, but of the 99 patients who had no gross bleeding before operation, 15 per cent have had subsequent bleeding. These clinical data would tend to support the belief that if splenectomy were performed early in the course of the disease before the development of esophageal and gastric varices, bleeding could be prevented in a large percentage of cases of Banti's syndrome.

After the demonstration by Crafoord and Frenckner in 1939 that esophageal varices could be obliterated safely by the injection of sclerosing solution, my colleague, Dr. Herman Moersch, has employed this method of treatment in a series of patients who had recurrent bleeding after splenectomy. Doctor Moersch has kindly furnished me with a brief summary of the results of injection of the esophageal varices in 22 cases in which patients were treated up to three years ago. Twelve patients were completely relieved of their bleeding. These patients have been followed up for from four to six years. Apparently in all these cases the varices were confined to the esophagus. The results in the remaining ten cases were unsatisfactory. In all ten, varices were demonstrable in the cardiac end of the stomach, as well as in the esophagus. The results are as follows: Three patients died of further bleeding; one patient died, cause unknown; one patient died of cerebral hemorrhage; one patient died of hepatic insufficiency, and four patients are alive but have had further bleeding.

Doctor Moersch feels, therefore, that the injection is an effective method of preventing bleeding in those cases in which the varices are limited to the esophagus, but that it is of little or no value in those cases in which the varices extend into the cardiac end of the stomach. It is for patients in this latter group of cases that further measures are needed in order to prevent bleeding, and I believe that Doctor Phemister's procedure is a logical approach to the problem. It may appear too radical, but I am convinced that any procedure, however formidable, which offers any reasonable hope for these patients is definitely warranted. I want to congratulate Doctor Phemister.

DR. ARTHUR H. BLAKEMORE, New York City: On the basis that in cases having portal hypertension, the most frequent sites of hemorrhage are from gastric veins and esophageal varices, Doctor Phemister and his associate have removed the stomach and lower esophagus in two cases.

Such a procedure obviously deals effectively with any varicosities existing within the limits of the resection, but fails to correct the underlying cause. In re-establishing the continuity of the alimentary tract, Doctor Phemister has anastomosed the esophagus to the jejunum. The venous drainage from the esophagus is into the caval system via the azygos veins. The venous drainage of the jejunum is into the portal system. At the site of the anastomosis, branches of the caval system inosculate with branches of the portal system and, in the presence of portal hypertension, the subsequent development of varices is inevitable.

In the past, radical excisions of the inosculating system of portal and caval branches has failed to relieve hemorrhage in the presence of portal hypertension.

DR. DALLAS B. PHEMISTER (closing): It should be emphasized that gastric or esophageal hemorrhage in Banti's Syndrome is usually the result of rupture of varices that lie immediately beneath the mucosa or even extend out into its substance, and that it is not associated with the deeper and more extensive ulceration mentioned by Doctor Wangenstein, which is met with in the ulcer patient or in ulcers produced experimentally in animals by histamine implantation.

Doctor Blakemore has pointed out that gastro-esophageal resection throws an extra load on the other points of collateral circulation. This is true, but they rarely ever bleed. For example, I have not seen bleeding hemorrhoids in a patient with Banti's Syndrome. Consequently, resection may be justified.

ACUTE CHOLECYSTITIS FOLLOWING THE SURGICAL TREATMENT OF UNRELATED DISEASE*

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ACUTE CHOLECYSTITIS following surgical operations other than on the biliary tract has attracted the occasional attention of surgeons for some time. Vest¹ reported a case from the Union Memorial Hospital in Baltimore of a 22-year-old woman who was operated on for subacute appendicitis. Palpation of the gallbladder at operation was reported normal. She made an uneventful recovery and was discharged a week after operation. Three days later she was seized with sudden intense pain in the upper abdomen associated with marked spasm and tenderness in the gallbladder region. A gallbladder containing large amounts of black bile and a single mulberry stone was removed after readmission to the hospital. Fisher² reported another case from Baltimore of a 19-year-old football player who was operated on for open reduction of the scaphoid. Two days later he developed manifestations of acute cholecystitis with a white count of 17,200. At operation a gangrenous gallbladder was removed and the patient made an uneventful recovery. One of the earliest cases in the literature was reported by Duncan³ in 1844. The patient was a woman with a strangulated hernia of 24 hours' duration and general symptoms of intestinal obstruction. The hernia was easily reduced but the symptoms became more severe and suggestive of peritonitis. Death occurred in 48 hours. Postmortem showed the under-surface of the gallbladder to be gangrenous; it had perforated, resulting in bile peritonitis. No stones were found. Another instance was reported by Kocher⁴ of a 51-year-old woman who developed acute symptoms of cholecystitis eight days after repair of a ventral hernia. At operation a gangrenous gallbladder was found.

Several years ago I saw at autopsy a patient who had died because of a generalized peritonitis secondary to an acute gangrenous cholecystitis with a free perforation into the peritoneal cavity. The patient was a 60-year-old male who had been operated upon for repair of a large sliding hernia that contained much of the sigmoid colon. He was obese, weighing 74.2 kilos. The operation was done without difficulty under spinal anesthesia. Because of the dissection required to liberate the incarcerated bowel, the patient after operation was maintained on clear liquids by mouth and infusions for six days. The diet was then increased and on the seventh postoperative day he complained of abdominal pain that was first generalized and then became most marked on the right side. This was accompanied by an elevation of temperature to 38° C., an increase in the pulse rate to 100, and marked abdominal distention. The latter was only partially relieved by enemas. Nausea and vomiting were marked on the 9th postoperative day and a flat plate revealed

* Read before the American Surgical Association, March 25, 1947, Hot Springs, Va.

marked large bowel distention. Because of these symptoms and findings, a laparotomy was done ten days after repair of the hernia and particular attention was directed to the left colon which had been incarcerated in the large hernia. The fluid in the abdomen was blood-tinged and the lower bowel was distended but otherwise not unusual. The region of the gallbladder was not examined, although a colostomy of the transverse colon was done in an effort to relieve the bowel distention. Five days later the patient died. The gangrenous gallbladder containing stones had perforated into the peritoneal cavity, resulting in a generalized peritonitis, the cause of death.

Over a period of 14 years (from September 1, 1932, to September 1, 1946), at the New York Hospital, a total of 555 patients have been operated upon for acute cholecystitis. This phase of gallbladder disease, we feel, is well treated by surgery and for those patients under 50 years of age the operative mortality has been low, there having been four deaths, a mortality rate of 1.08 per cent in a group of 368 patients. The mortality rate was much higher in the 187 patients over 50 years of age; there were 11 deaths, a mortality rate of 6.1 per cent. During this same period over 2,000 patients were operated upon for non-malignant disease of the biliary tract.

TABLE I
ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL
September 1, 1932, to September 1, 1946

Total cases.....	555
Deaths.....	15
Mortality, per cent.....	2.7
Operative Procedures	
Cholecystectomy.....	485
Cholecystostomy.....	70*
Common duct exploration.....	44

* 12.6% of total operations.

Cholecystostomy was performed in 70 instances and was followed by six deaths. This procedure is clearly indicated under certain circumstances, as when the patient is too ill to withstand cholecystectomy or when cholecystectomy presents too great difficulties. For the extremely debilitated patient or for the very ill, we doubt if there are any contraindications for cholecystostomy because it may be done under local anesthesia, disturbing the patient very little, and at the same time the simple procedure may be a life-saving one. The decompression of the biliary tract averts catastrophe by preventing progressive liver damage if complete biliary obstruction is present.

TABLE II
ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL
September 1, 1932, to September 1, 1946
Patients fifty years of age or over

Total cases.....	187
Deaths.....	11
Mortality, per cent.....	6.1
Operative Procedures	
Cholecystectomy.....	150
Cholecystostomy.....	37*
Common duct exploration.....	24

* 19% of total operations.

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In the series of 555 patients treated surgically, 187 were 50 years of age or over. There were 11 deaths, a mortality rate of 6.1 per cent. One hundred and fifty were subjected to cholecystectomy. Thirty-seven, or 19 per cent of the 187, were treated by cholecystostomy. Twenty-four, had in addition to these operations, exploration of the common duct. The mortality rate of 6.1 per cent of these patients who were 50 years of age and over indicates the definite greater risk associated with them than those of less than 50 years of age with a mortality rate of 1.08 per cent.

TABLE III
ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL
September 1, 1932, to September 1, 1946
Patients under fifty years of age

Total cases.....	368
Deaths.....	4
Mortality, per cent.....	1.08
Operative Procedures	
Cholecystectomy.....	334
Cholecystostomy.....	33*
Common duct exploration.....	26

* 9% of total operations.

The remaining 368 of the 555 patients were under 50 years of age. There were four deaths, a mortality rate of 1.08 per cent. Three hundred and thirty-four, or 90.8 per cent, were subjected to cholecystectomy, and 33, or 8.9 per cent, were treated by cholecystostomy. Only 26, or 7.1 per cent, had in addition to one of the above procedures, exploration of the common duct. This is a far more favorable outcome than our experience with the group of patients who were 50 years and over.

During this period of 14 years I have observed 17 patients who developed acute cholecystitis following a surgical procedure unrelated to the biliary tract. They are as follows:

Diagnosis	Number Cases	Age of Patients
Hernia	4	60-62-60-58
Acute appendicitis	2	67-32
Hemorrhoids	2	60-58
Hydrocele	1	63
Fissure in ano	1	54
Ovarian cyst	1	29
Abscess of leg	1	67
Nasal packing for epistaxis	1	41
Bladder stones, hypertrophy of prostate	1	64
Tumor of salivary gland	1	63
Hypertrophy of the prostate	1	54
Carcinoma of the rectum	1	49
Total	17	

Five of these patients were observed during the last part of 1945 and 1946. Their case summaries are presented as illustrative of the common course of events.

Case 1: C. S.—#438487. This 67-year-old white male was admitted to the hospital because of a cellulitis superimposed upon dependent edema of the lower extremities secondary to cardiac disease. The cellulitis had followed a severe sunburn sustained in Florida. He was admitted to the hospital, placed at rest in bed, and digitalized. During this period he developed a subcutaneous abscess that was incised and drained under local anesthesia. He received morphine and codeine for discomfort and because of his cardiac condition was placed on limited intake by mouth. He received penicillin for his infection. Eight days after admission and two days after incision and drainage of the abscess, he suddenly developed pain in the right side of his abdomen associated with nausea and vomiting. There was no history of any similar previous episodes. His temperature within a few hours was 38.4° C. and his white count rose to 22,300. The entire right side of the abdomen was held so rigid that no masses could be palpated. A diagnosis of probable acute cholecystitis was made and under local anesthesia a cholecystostomy was done. There was bile-stained fluid free in the peritoneal cavity; the gallbladder was tense and acutely inflamed. It contained white bile and bile-stained material but no stones. The patient's postoperative course was satisfactory. Because of his cardiac condition he was discharged from the hospital and died some weeks thereafter of cardiac disease.

Case 2: S. G.—#461002. A 32-year-old male was operated upon for acute suppurative appendicitis with gangrene, having had symptoms for about three days prior to operation. Following the appendectomy the patient received nothing by mouth for several days because of peritonitis; morphine was given for pain. He had glucose infusions up to 3,000 cc. per day. He was a somewhat apprehensive individual who was very slow in resuming a normal intake by mouth. Solid food was first taken on the 9th postoperative day; the next day he complained of pain in the right upper quadrant which gradually increased in severity. He became nauseated and vomited, and associated with this was an elevation of temperature to 37.8° C. and of the white count to 24,000. At operation a large, acutely inflamed gallbladder containing 50–60 stones was removed. His postoperative course was entirely satisfactory and he was discharged two weeks later. It is probable that the prolonged period of fasting and a moderate amount of drug therapy may have precipitated this acute attack.

Case 3: C. R.—#446343. A 62-year-old man was admitted to the hospital for repair of an indirect inguinal hernia. In the course of a check-up cholecystograms were taken, revealing stones. The patient was operated upon for repair of the hernia under local anesthesia, having been given preoperative morphine, and clear fluids were given immediately after operation. He received morphine on the first postoperative day and codeine on the second, and he was then placed on a soft diet. On the third day he complained of severe pain in the right upper quadrant following the taking of a few bites of creamed shrimp. Within a few hours there was a palpable mass in the right upper quadrant which was believed to be the gallbladder. His white count was 12,000 and his temperature rose to 38.4° C. He was nauseated and vomited. A diagnosis of acute cholecystitis was made and operation recommended but refused by the patient. The acute episode gradually subsided over a period of three days and the patient was discharged from the hospital to return four months later when a gallbladder containing many stones was removed.

Case 4: F. C.—#403668. A 41-year-old hotel executive was admitted to the hospital because of epistaxis which was severe and persistent. His past history was significant. Eight years before he had had acute cholecystitis, and a cholecystostomy was done and stones removed. Six years later because of indigestion he had had cholecystograms done which revealed a poorly functioning gallbladder containing stones. For years he had taken several cocktails and highballs each day. His prothrombin time was prolonged but became normal following the administration of vitamin K. Upon admission to the hospital he was given transfusions. Repeated packing of the left nostril was necessary

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and during this period the patient received morphine for pain and discomfort. Fluids were taken with difficulty and he received infusions; he took no food. He was running an elevated temperature of 39.8° C. which gradually subsided over the first five days of hospitalization, at the end of which time he was greatly improved. His temperature was almost normal and he received solid food for the first time on the 5th day after admission. Shortly thereafter the patient had severe right upper quadrant pain radiating around the right costal margin. He was nauseated but did not vomit. Within a few hours the entire abdomen had become rigid to examination, the pulse was elevated to 120, the temperature to 39.4° C., and the white count to 13,000. It was the impression of the author that the patient had a perforation of the gallbladder associated with acute cholecystitis. He was subjected to immediate operation but because of his poor general condition only a cholecystostomy was done for acute gangrenous cholecystitis with a perforation through which bile was escaping. There was a single stone which was removed. He was discharged from the hospital 22 days later. Four months thereafter he was readmitted and a cholecystectomy was done.

Case 5: P. H.—#455952. A 64-year-old male was admitted to the hospital because of a bladder stone and hypertrophy of the prostate. The patient had in addition to his urinary symptoms some indigestion, and prior to operation a cholecystogram was taken which revealed stones. Seven days after admission a suprapubic cystolithotomy and suprapubic prostatectomy were performed under spinal anesthesia. He received pre-operative morphine and also morphine after operation, as well as parenteral fluids. During the following six days the patient was without appetite and took only clear fluids. On the 7th postoperative day he began to take his first solid food. The following day he complained of pain in the right upper quadrant and was nauseated but did not vomit. Over a period of 12 hours there developed a mass in the right upper quadrant and generalized muscular resistance of the right rectus. His temperature rose to 38.8° C. and the white count was 14,200. The patient was operated on and an acutely inflamed, distended gallbladder was found which contained a large stone in the ampullary region. Because the patient had at the time of this operation an upper respiratory infection as well as some elevation of his urinary nitrogen, the operation was performed under local anesthesia and only a cholecystostomy was done. Following this procedure he made an uneventful recovery and was discharged from the hospital on the 25th postoperative day. He is to return for cholecystectomy.

Because of the controversy commonly associated with the early surgical treatment of acute cholecystitis, we have been constantly reviewing our experience in an attempt to evaluate properly our policy. Our aim has been to interrupt biliary disease early by surgical interference. Acute cholecystitis is but a phase of biliary tract disease. It is an important phase, however, because in it certain complications may arise which are associated with a high mortality rate. And it has been reported again and again in the literature that these complications and their accompanying mortality account for a very definite proportion of the deaths that result from operations upon the gallbladder and bile ducts. In a paper entitled "The Factors Leading to Death in Operations Upon the Gallbladder and Bile Ducts," Heuer⁵ in 1934 reported that 20 authors up to that time had recorded 502 instances of perforation of the gallbladder. Only eight of these recorded their mortality figures; however, these ranged from 33.3 to 100 per cent. In a review of the literature from 1934 to 1946 I have found reports of 25 authors who have recorded an additional 457 cases. Twenty-two of the 25 authors have given their mortality figures and these range from 5.8 per cent to 75 per cent.

TABLE IV
GALLBLADDER PERFORATIONS FROM THE LITERATURE—DEATHS AND MORTALITY
Heuer—1934

Author and Reference	Number		Mortality (Per Cent)
	Cases	Deaths	
Blalock, A.: Bull. Johns Hopkins Hosp., 35:391, 1924....	21	?	
Smith, M.: Tr. Am. S. A., 51:287, 1933.....	24	?	
Johnson: South. M. J., 19:889, 1926.....	9	9	100.0
Judd, Parker: Ann. Surg., 84:419, 1926.....	2	?	
Siegmund: Deutsches Arch. f. Chir., 230:359, 1924.....	8	5	62.5
Heuer, G.: West Virginia M. J., 26:1, 1930.....	18	?	
Danzia: S. Clin. North America, 6:1397, 1926.....	1	1	100.0
Stanton: Am. J. Surg., 8:1026, 1930.....	32	32	100.0
Santee: Ann. Surg., 93:1156, 1931.....	5	3	60.0
Alexander: Ann. Surg., 86:765, 1927.....	20	?	
Mitchell: Ann. Surg., 88:200, 1928.....	16	?	
McWilliams: Ann. Surg., 55:235, 1912.....	6	2	33.3
McWilliams: Ann. Surg., 55:235, cites.....	108	52	48.0
Gosset, Deplas: J. de chir., 25:259, 1925.....	111	?	
Darner, Cullen: Surg., Gynec. & Obst., 37:579, 1923.....	3	2	66.6
Zinninger: Ann. Surg., 96:406, 1931.....	16	?	
Miller: Ann. Surg., 92:644, 1930.....	8	?	
Graham: Ann. Surg., 93:1152, 1931.....	7	?	
Judd, Phillips: Tr. Am. S. A., 51:292, 1933.....	68	?	
Mentzer: Surg., Gynec. & Obst., 55:709, 1932.....	19	?	
Total.....	502		

TABLE V
PERFORATION OF THE GALLBLADDER—ADDITIONAL CASES FROM THE LITERATURE
Glenn—1947

Author and Reference	Number		Mortality (Per Cent)
	Cases	Deaths	
Cowley & Hawkins: Surg., Gynec. & Obst., 77:661, 1943..	25	4	24.0
Edwards & Goerig: Ann. Surg., 113:824, 1941.....	18	3	16.6
Stone & Douglas: Am. J. Surg., 45:301, 1939.....	17	1	5.8
Eliason & McLaughlin: Ann. Surg., 99:914, 1934.....	9	1	11.0
Niemeier, O.: Ann. Surg., 99:922, 1934.....	8	0	0
Sanders, R.: Surgery, 1:949, 1937.....	46	8	17.4
Noble, T.: Am. J. Surg., 38:259, 1937.....	9	3	33.3
Bachhuber & Deeb: Am. J. Surg., 67:40, 1945.....	22	3	13.6
Johnston & Ostendorph: Arch. Surg., 53:1, 1946.....	3	0	0
Heyd, C. G.: Ann. Surg., 101:797, 1935.....	6	1	16.0
D'Abreu, A.: Brit. M. J., 2:1156, 1936.....	3	2	66.6
Hotz, R.: Am. J. Surg., 44:706, 1939.....	53	19	35.8
Atlee, J. & Atlee, J., Jr.: Pennsylvania M. J., 44:731, 1941	15	3	20.0
Schaeffer, R.: Pennsylvania M. J., 45:566, 1942.....	20	8	40.0
Graham & Hoeffle: Ann. Surg., 108:874, 1938.....	4	3	75.0
Blain & Harkins: Surgery, 21:110, 1947.....	9	5	55.0
Blumberg, N., & Zisserman, L.: Am. J. Surg., 70:38, 1945..	21	7	33.3
Root & Priestley: Am. J. Surg., 61:38, 1943.....	22	8 ?	
Stout & Hibbard: Surgery, 13:734, 1943.....	6	4	66.6
Eliason & Stevens: Surg., Gynec. & Obst., 65:79, 1937...	17	0	0
Wallace & Allen: Arch. Surg., 43:762, 1941.....	64	11	17.2
Wesson, H.: Proc. Staff Meet., Mayo Clin., 12:500, 1943..	16	0	0
Taylor, F.: Surg., Gynec. & Obst., 63:298, 1936.....	15	3 ?	
Touroff, A.: Ann. Surg., 99:900, 1934.....	4	?	
Glenn & Moore: Arch. Surg., 44 (677-686), 1942.....	25	4	16.0
Total.....	447		

The genesis of acute cholecystitis following unrelated surgical operations may be accounted for as follows. The patient for a certain number of hours

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before operation receives nothing by mouth; he then receives preoperative medication of morphine and atropine. It is believed that the flow of bile from the liver into the gallbladder is almost constant—the preoperative medication does not alter this. The bile is concentrated in the gallbladder. The operation then takes place, and the flow of bile under anesthesia may be reduced, but the operation is a matter of one to a few hours. Then the flow of bile into the gallbladder begins again. There is further concentration of bile in the gallbladder until some stimulus in the stomach or duodenum results in its emptying. At first the patient usually takes water, then clear liquids, full liquids and then a soft diet. Upon ingestion of a soft diet there may be, for the first time, since water and food were withheld before operation, an all-out attempt on the part of the gallbladder to empty its viscid and concentrated bile into the common duct and thence into the duodenum. If a stone or stones block the escape of the concentrated bile from the gallbladder then the mechanism for obstructive cholecystitis obtains and an acute episode in the cycle of gallbladder disease may result. However, there are instances of acute cholecystitis in our experience without stones.

The pathology of the gallbladder in the patient who develops acute cholecystitis following a surgical procedure is indistinguishable from that observed in patients commonly encountered. In cholelithiasis the degree of ischemia or edema would appear to depend upon the location and relation of the cystic vein and cystic artery to the segment of the cystic duct or ampulla, within which is lodged the stone. The gallbladder which has had many previous episodes of inflammatory reaction is more scarred and therefore does not become distended and enlarged to the extent that the more normal gallbladder does. Likewise the thickness of the gallbladder wall is dependent upon the amount of edema that may be the result of obstruction to the venous return and the nature and extent of the bacterial infection within the gallbladder wall. Certain types of infection, of short or long duration, tend to produce a great deal of reaction with the result that the thickness of the gallbladder wall is several times that of the normal organ. The thickness of the wall might determine to some degree the readiness with which perforation would take place, providing the type of infection were equal in the two. The rapidity with which gangrene develops and is followed by perforation is dependent upon the interference of the blood supply, the rapidity with which the infection takes place, and the virulence of the organism and its capacity to cause necrosis.

We would not imply that free perforation is to be anticipated in the majority of patients with acute cholecystitis. The omentum and its tendency to become attached to the inflamed gallbladder wall constitutes a normal protective mechanism, and it is probable that this comes into effect in the majority of patients. If the area of gangrene in the gallbladder wall is limited to the fundus, then attachment of the omentum may block the free escape of bile into the peritoneal cavity. If, however, the entire organ is involved, then it is probable that the omentum will be unable to protect the peritoneal cavity. Where there has been a free escape of bile into the abdominal cavity, there is

usually an absence of any pretext of adhesions between the gallbladder wall and the omentum. Whether or not this is due to the action of the bile or whether there is some other process with which we are not familiar that prevents it fulfilling its normal function is not known. In late bile peritonitis the omentum as a rule seems to be contracted and much smaller, and assumes the normal position down over the mid-portion of the abdomen rather than traveling to the source of the bile leakage.

In discussion of the treatment of acute cholecystitis with those who favor nonoperative treatment, we are often confronted with the statement that perforation of the acute gallbladder rarely, if ever, occurs. Our experience at the New York Hospital and that reported by other clinics suggest that it is much more common than is generally accepted.

Johnstone and Ostendorph⁶ found on review of 12,000 consecutive routine autopsies done at the Los Angeles Hospital from 1936 to 1942 a total of 32 instances of perforation of the gallbladder as the principal cause of death. This is an incidence of 0.26 per cent, or approximately one out of every 375 cases coming to autopsy. This is the highest incidence of perforation that has been reported. Nineteen, or 43 per cent of these cases, were free perforations which without evidence of walling off had led to generalized peritonitis. Almost two-thirds of these patients were 50 years of age or more. They also found that there was a much higher proportion of male patients, 22, or 68 per cent of the patients, being men. This is of suggested importance in the consideration of the cases reported above, because all but one of these patients developing acute cholecystitis following operation unassociated with the biliary tract, were men.

Green and Coe⁷ report perforation of the gallbladder occurring twice in the same patient. Cholecystostomy was done for the first perforation. The second perforation was followed by death. This was a free perforation of the gallbladder with an estimated 100 cc. of bile in the peritoneal cavity. The site of perforation was adjacent to an old sinus communicating with the fundus of the gallbladder. To all intents and purposes, therefore, it was a perforation at the same site, and in both instances the attacks were associated with pain radiating to the right shoulder as well as pain and tenderness in the right upper quadrant. Both were rapidly progressive.

Acute cholecystitis may be unrecognized as a complication following surgical procedures. The incidence of cholelithiasis in the population is rather large. This is especially true of those patients who are over 50 years of age. Our surgical armamentarium has resulted in an increase in the number of patients in the older age group who are daily operated upon throughout the country. The onset of pain in the abdomen localizing in the right upper quadrant, usually associated with nausea and vomiting and accompanied by some elevation of temperature and leukocytosis, would seem sufficient to make this diagnosis relatively certain. Of significance in evaluating the immediate situation is the patient's past history relative to biliary tract disease. Indeed, the patient over 50 years of age who is to undergo a major surgical procedure

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for a condition unrelated to the biliary tract should have a careful evaluation of his history to determine any symptoms referable to this system. If the history is suggestive of biliary tract disease, it is well to do a cholecystogram to determine the presence or absence of cholelithiasis and the capacity of the gallbladder to fill and concentrate the dye as well as its ability to empty. Then if a patient develops the symptoms of acute cholecystitis after operation it is less likely to be overlooked if stones are known to be present.

Once the diagnosis has been established, the therapy to be accorded the patient will be determined by a number of factors. Our experience over the past 14 years at the New York Hospital justifies, it seems to us, early surgical therapy. A patient who has been operated upon and who is suffering from acute cholecystitis as a complication may not in many instances be an ideal surgical risk. It is to be expected that there will be many patients in whom cholecystectomy is contraindicated. On the other hand, there can be no contraindications to cholecystostomy done under local anesthesia. This is a minimal procedure; it is also one which may be life-saving. There are many patients, perhaps in the majority, who will recover from this attack. Many patients will refuse a second operation, and there are those for whom the surgeon will be reluctant to recommend even a cholecystostomy for one reason or another. In the relatively young patient the risk associated with non-surgical treatment is, we feel, much less than in the older age group. In those patients who are over 50 years of age the temperature, leukocyte count, and even the clinical picture frequently do not parallel the pathologic process which is taking place within the gallbladder. It is in this group in particular that we feel early surgery is imperative.

If a cholecystostomy is done it should be followed in a matter of months, with the patient as well prepared as possible, by a cholecystectomy. In this respect, the report of Green and Coe describing a patient who had an acute cholecystitis with perforation treated by cholecystostomy and who recovered and then years later experienced another episode of acute cholecystitis with perforation followed by death, is significant. One of the patients listed above (F. C.—#403668) developed an acute cholecystitis associated with a large stone impacted in the ampulla of the gallbladder eight years after cholecystostomy. These two cases are evidence in favor of cholecystectomy being done within a reasonable period after the compromise procedure of cholecystostomy.

CONCLUSIONS

Acute cholecystitis may occur after surgical procedures, especially in male patients who are over 50 years of age. When it does the best interests of the patient require operation. This may be cholecystectomy or cholecystostomy. The procedure is determined by the patient's condition. It will frequently be found that cholecystectomy may be inadvisable and that only a cholecystostomy can be done. This procedure may, however, be life-saving. Cholecystectomy should be done later; cholecystostomy is but a compromise procedure. It is no insurance against future episodes of acute cholecystitis or accompanying perforation that may well end fatally.

REFERENCES

- ¹ Vest, S. A., Jr.: Gangrene of the Gallbladder; *Internat. Surg. Digest*, **15**, 131-160, 1933.
- ² Fisher, W. A.: (Quoted by S. A. Vest, Jr.: Gangrene of the Gallbladder; *Internat. Surg. Digest*, **15**, 131-160, 1933.)
- ³ Duncan, J.: Femoral Hernia: Gangrene of the Gallbladder; Extravasation of Bile; Peritonitis; Death. *North. J. Med.*, **2**, 151-153, 1844-1845.
- ⁴ Kocher, T., and H. Matti: Ueber 100 Operationen an den Gallenwegen mit Berücksichtigung der Dauererfolge; *Arch. f. klin. Chir.*, **81**, 655, 1906.
- ⁵ Heuer, George J.: The Factors Leading to Death in Operations Upon the Gallbladder and Bile-Ducts. *ANNALS OF SURGERY*, **99**, 6, 1934.
- ⁶ Johnstone, G. A., and Ostendorph, J. E. *Arch. Surg.*, **53**, 1, 1946.
- ⁷ Green, E. I., and George C. Coe: Acute Free Perforation of the Gallbladder Occurring Twice in the Same Patient. *Surgery*, **7**, 396-400, 1930.

DISCUSSION.—DR. HENRY F. GRAHAM, Brooklyn, N. Y.: I have had the pleasure of reading this paper in advance, so my discussion is a little prepared.

Dr. Glenn's theme seems to be (1) Acute cholecystitis is more apt to occur as a complication following operation for other conditions than its normal incidence as a primary disease. (2) It is more apt to occur in elderly people past 50 and in males. (3) He mentions, as a possible explanation of its occurrence, dehydration and medication which decreases secretion and causes concentration of thickened bile in the gallbladder which cannot easily be expelled upon food stimulation. This is an interesting hypothesis but might be open to question in view of the types of cases where operation has been followed by acute cholecystitis. I am convinced, however, that in many patients large doses of sedatives do have a deleterious effect. (4) The diminished resistance of the gallbladder to pressure and infection following previous disease may favor perforation. It would be easy for each of us to prove this by a review of his own records, and it would not be without chagrin if we look up those cases we have forgotten.

I checked up on three cases. One was a woman aged 56 who had an operation for appendiceal abscess. Sixteen days later she complained of pain around the waist line and had induration of the epigastrium and right upper quadrant. The appendiceal wound showed thick yellow pus. A high temperature was thought to be due to sulfonamides. The attack subsided after 12 days. Two weeks later she had another attack with pain in the upper quadrant, tenderness and vomiting. Empyema of the gallbladder was found at operation. Another case was a man aged 45, who had suffered from epigastric pain for six months with a loss of 40 pounds in weight. On his third day in the hospital, while being studied preparatory to operation for duodenal ulcer, he had a sudden attack of pain in the lower abdomen following an enema. The leukocyte count was 14,000. X-rays were taken to visualize free air under the diaphragm and, finally, after 24 hours delay, because of the confused picture a cholecystostomy was performed for a perforated gallbladder.

A physician, 72 years old, was under treatment for coronary thrombosis and acute diffuse nephritis. After six weeks in the hospital he had pain in the gallbladder region. He was observed for three weeks because of his poor condition. Operation then disclosed an empyema of the gallbladder with a sealed-off perforation covered by omentum.

This paper should stimulate an increased awareness of acute cholecystitis complicating other diseases and especially following operation for other conditions.

A CONSIDERATION OF PATHOLOGICAL FACTORS INFLUENCING FIVE YEAR SURVIVAL IN RADICAL RESECTION OF THE LARGE BOWEL AND RECTUM FOR CARCINOMA*†

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THIS IS A STUDY of 200 patients operated upon more than five years ago for carcinoma of the large bowel where there was a reasonable chance of cure. All of the surgical specimens were cleared and the lymph nodes were dissected under transillumination and the microscopically involved nodes were charted by a method reported to this society in 1938.¹ The specimens used in this analysis were not always consecutive due to the work involved in the study of each one but were otherwise unselected except that the specimens from all fatalities were included. This results in somewhat higher mortality figures and lower five-year survival rates.

These 200 patients represent an operability rate of approximately 75 per cent. Palliative resections for removal of tumor where known metastases could not be removed are not included in this group.

TABLE I
200 CASES OF CARCINOMA OF THE COLON

	Per Cent
125 had lymph node metastases.....	62.5
114 alive 5 to 10 years.....	57.0
19 postoperative (hospital) deaths.....	9.5
8 died 1 to 5 years—not carcinoma.....	4.0
7 incomplete follow-ups.....	3.5

There is need for accurate anatomic location of tumors when discussing treatment of carcinoma of the rectum. The term "rectosigmoid junction" means different things to different surgeons. It can be located fairly accurately on proctoscopic examination. However, it is impossible to identify on a surgical specimen. Roentgenologists often consider it a region two or three inches in length. This study has demonstrated the very different prognosis, recurrence, and mortality rate in different regions of the colon. It seems to us that a new set of landmarks should be used. We have designated those carcinomas which are partially or completely below the peritoneal reflection as "extraperitoneal carcinoma of the rectum." There were 112 of these. Those lesions which are entirely covered by peritoneum, anteriorly, and which are below the promontory of the sacrum should be designated as "intraperitoneal carcinoma of the rectum." There were 41 of these. Fourteen were in the redundant loop of sigmoid above the promontory of the sacrum. (These last two—total of 55—will be grouped as one in this discussion as all findings

* Read before the American Surgical Association, March 25, 1947, Hot Springs, Va.

† Funds for this investigation were obtained from the Otho S. A. Sprague Memorial Institute Fund of the Presbyterian Hospital.

were identical.) Fifteen were in the right colon, which included the cecum, ascending colon, hepatic flexure and the first three inches of the transverse colon. Eighteen were in the left colon, which included all of the remainder of the colon to the redundant loop of the sigmoid.

One hundred and twelve tumors were partially or completely below the peritoneal reflection. There were 12 postoperative deaths and four had no follow-up. Only 26 of the 69 with node metastases were alive after five years (37.5 per cent), whereas 32 of the 43 without node metastases were alive five years (74.4 per cent).

TABLE II

112 EXTRAPERITONEAL RECTAL CARCINOMAS

	Per Cent
58 alive 5 to 10 years.	51.8
12 postoperative deaths.	10.7
69 had lymph node metastases.	61.9
26/69 with node metastases alive 5 years.	37.5
32/43 without node metastases alive 5 years.	74.4

Of the 69 with node metastases, 30 or 43.5 per cent developed recurrent carcinoma in less than five years while only five or 11.6 per cent of the 43 without involved nodes developed recurrent carcinoma.

TABLE III

112 EXTRAPERITONEAL RECTAL CARCINOMAS

Recurrence	69 With Node Metastases		43 Without Node Metastases	
Local.	16	23.2%	2	4.6%
Liver.	11	15.9%	2	4.6%
Lung, bone, general.	3	4.3%	1	2.3%
	30	43.5%	5	11.6%

The incidence of local and liver recurrences in these low lying tumors is striking.

Fifty-five tumors were entirely above the peritoneal reflection. Fourteen were in the sigmoid and 41 were below the promontory of the sacrum. All findings were identical and these were grouped to save space. The favorable prognosis in this group and especially in those without lymph node metastases (90 per cent), is striking.

Twenty-seven of the 55 patients had obstruction resections performed. In many, the extraperitonealization of the resected area was done as described by David.³ In the more unfavorable cases, abdominoperineal resections were performed. This probably accounts for the fact that the results with obstruction resections were about the same as with the abdominoperineal resections. 18.1 per cent of the 55 died of recurrence within five years, the recurrence rates being similar in the two types of operations. The low incidence of

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recurrence here contrasts sharply with the 43.5 per cent seen in tumors which are extraperitoneal.

TABLE IV
55 INTRAPERITONEAL RECTAL AND SIGMOID CARCINOMAS

	Per Cent
36 alive 5 years.....	65.4
4 postoperative deaths.....	7.2
3 deaths not due to carcinoma.....	5.5
2 had no follow-ups.....	3.6
35 had node metastases.....	63.3
18 with node metastases alive 5 years.....	51.4
20 had no node metastases	
18 without node metastases alive 5 years.....	90.0
1 no follow-up	
1 postoperative death	
27 obstruction resections	
18 alive 5 years.....	66.6
16 had node metastases	
9 with node metastases alive 5 years.....	56.2
2 postoperative deaths	
1 short follow-up	
11 without node metastases	
9 without node metastases alive 5 years.....	81.9
1 postoperative death	
1 no follow-up	

TABLE V
RECURRENCES IN 55 INTRAPERITONEAL TUMORS

	No. Patients	Per Cent
Local.....	2	3.6
Liver.....	6	10.9
Lung or general.....	2	3.6
Total.....	10	18.1

Resections of the 33 patients with carcinoma proximal to the sigmoid colon were done by several different surgeons. Twenty-one had lymph node metastases (63.6 per cent). Twenty were alive five or more years (60.6 per cent). There were three with carcinoma of the cecum and with metastases to nodes who died after operation (9.1 per cent). One was lost to follow-up.

Fifteen were in the right colon; all had ileotransverse colon anastomoses at the time of resection. Thirteen or 86.6 per cent of these had metastases to nodes and, in spite of three postoperative deaths and one lost to follow-up, nine were known to be alive after five years (61.5 per cent). These operations were performed before the era of chemotherapy; therefore, the operative mortality in this group would be lower at this time.

TABLE VI
15 TUMORS OF RIGHT COLON
ALL WITH ILEOTRANSVERSE COLON ANASTOMOSES

	Per Cent
9 alive 5 years.....	60.0
13 had involved nodes.....	86.6
7 with involved nodes alive 5 years.....	53.8
3 postoperative deaths	
1 had no follow-up	

Eighteen tumors were in the transverse or descending colon or at the splenic flexure. Only eight had node metastases (44.4 per cent). This is the lowest incidence of involved nodes seen. Five of these eight died of recurrence within five years. Only three of the eight lived five years (37.5 per cent) in contrast to 80 per cent of those without involved nodes. All of these had obstruction resections. There were no postoperative deaths and one was lost to follow-up. This suggests that resection in this area has been too conservative.

TABLE VII
18 TUMORS OF LEFT COLON
ALL OBSTRUCTION RESECTIONS

	Per Cent
11 alive 5 years.....	61.1
8 had involved nodes.....	44.4
3 with involved nodes alive 5 years.....	37.5
No postoperative deaths	
8/10 without nodes alive 5 years.....	80.0

The surgeon gave a guarded prognosis at the time of resection because of grossly enlarged lymph nodes in 55 of the 200 cases. This chart indicates the prognosis in those having palpably enlarged nodes which are proven to have metastases on microscopic section.

TABLE VIII
55 OF 200 GIVEN GUARDED PROGNOSIS DUE TO LARGE NODES

Location of Tumor	Alive 5-10 Yr.	Died 0-5 Yr.	P. Op. Deaths	Liver	Recurrences Local	Gen.	Deaths Not Ca.	Total Patients
Extraperitoneal								
With nodes.....	5	16	3	8	6	1	2	21
Without nodes.....	2	1					1	3
Below promontory								
With nodes.....	6	10		5	1	3	1	16
Without nodes.....	6							6
Colon								
With nodes.....	4	5	2	—	—	2	—	9
	23	32	5	13	7	6	4	55

Small scars ("grains of sand" nodules) were palpated in the liver in 11. These were too small and indefinite to be considered metastases. Eight lived five years. One died postoperatively. One developed a local recurrence and one died of diabetes where there was no recurrence. These small lesions are usually almost of one size and the occasional operator should not be influenced adversely when they are found.

TABLE IX
POOR PROGNOSIS DUE TO SUSPICIOUS NODULES IN LIVER—11

8 alive 5 to 10 years
3 died in less than 5 years
1 postoperative death
1 local recurrence
1 diabetes, not carcinoma.

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Thirty-five of the 200 patients required resection of all or part of other structures because of firm fixation of the tumor.

TABLE X
35 CARCINOMAS REQUIRING RESECTION
OF ALL OR PART OF OTHER STRUCTURES

	No. Pts.	Well 5-10 Yr.	P. Op. Deaths	Local	Recurrence Liver	Gen.	No Follow-Up
Presacral fascia.....	8	3	2	3			
Abdominal wall.....	4	3			1		
Ureter and bladder.....	9	2	3	1	2		1
Vagina.....	6	3	1		1	1	
Urethra and prostate.....	3	1		2			
Uterus.....	3		1	1	1		
Bowel.....	2	2					
	35	14	7	7	5	1	1

Fourteen or 40 per cent of these patients were well five years. This figure would be higher today as seven or 20 per cent died postoperatively and this mortality would be favorably influenced by chemotherapy. Wide excision of structures adherent to the tumor is justified by these findings.

Seven patients having carcinoma below the promontory of the sacrum had metastases to lymph nodes, distal to the tumor. This occurs when there is lymphatic blockade. This finding reemphasizes the necessity for extensive resection in those having enlarged nodes and large tumors.

TABLE XI
RETROGRADE METASTASES TO LYMPH NODES
IN CARCINOMA BELOW SACRAL PROMONTORY

2 with involved nodes	3.5 to 5 cm. below tumor
2 with involved nodes	2.5 to 3.5 cm. below tumor
3 with involved nodes	1.0 to 2.5 cm. below tumor

One hundred and forty had abdominoperineal resections of the rectum. Four of these were two-stage resections. In two, resections of other structures made a mass of tissue too large to pull through the pelvic outlet in the male and in these the rectum was cut off just above the anus and the stump closed. In all of these, there was an average of 55.3 nodes per specimen sectioned and studied microscopically. One specimen contained 210 nodes, and six had 112 or more nodes each. Those having an obstruction resection of the sigmoid or intraperitoneal rectum averaged 41.6 nodes per specimen and one specimen contained 102 nodes. Specimens from obstruction resection of the left colon averaged 40.2 nodes each and one had 69 nodes. Specimens of the right colon obtained by resection and primary ileotransverse colon anastomosis averaged 54 nodes each with one having 115. Seventy-two of the 125 specimens having metastases to lymph nodes had four or less nodes involved per specimen.

In low lying carcinomas of the rectum, small high lying lymph nodes not uncommonly are found to contain metastases. Figure 1 shows a specimen typical of such cases and serves to reemphasize the fact that the widest possible resection of the mesentery is needed to give a chance of permanent cure.

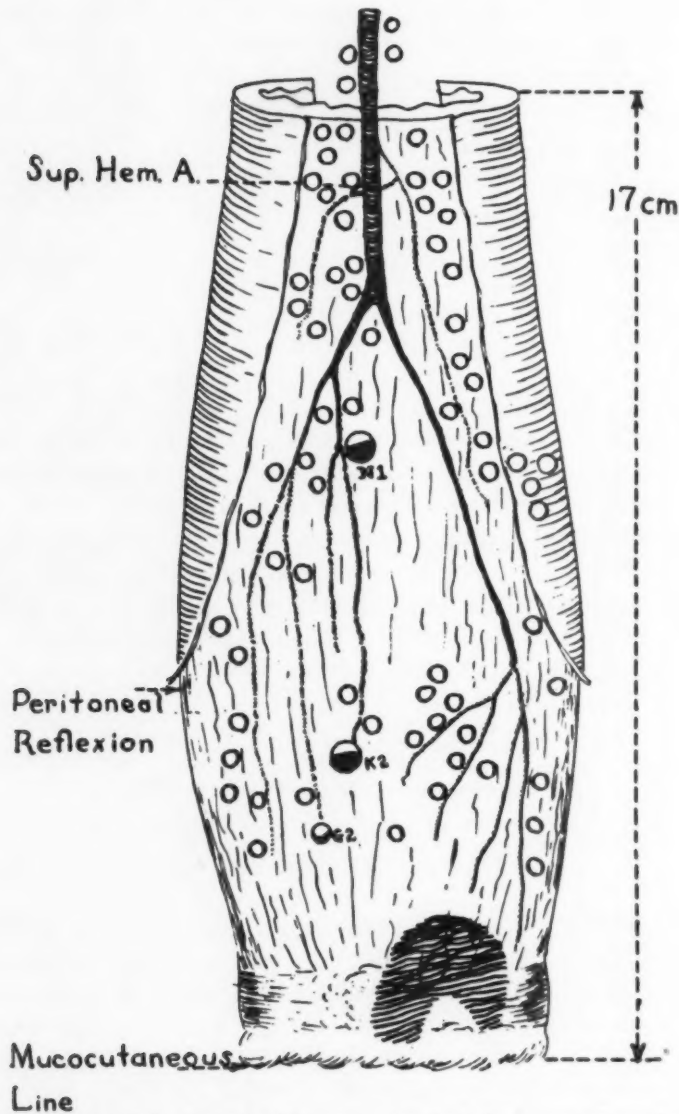


FIG. 1.—A 64-year-old man who had had symptoms for two months. This tumor was Grade III Broder's and Duke's C. He developed a local recurrence in the hollow of the sacrum within six months. This finding of metastases in nodes high above low-lying tumors is not uncommon even when only a few involved nodes are present. This seems to reemphasize the necessity for wide resection of mesentery even when there are no palpably enlarged nodes.

Nineteen died in the hospital after surgery. Eight had no postmortem examinations. Three had postmortem examinations and the usual search was made for metastases to retroperitoneal nodes but none were found although all three had had lymph node metastases in the surgical specimens. In the

LARGE BOWEL CARCINOMA

TABLE XII

Operation	Average Number Nodes	Most Nodes per Specimen
Miles.....	55.3	210
Obstruction Resection		
Sigmoid and rectum.....	41.6	102
Left colon.....	40.2	69
Right colon.....	54.0	115

4 or less involved nodes in 72/125 with involved nodes.

remaining eight, all of the retroperitoneal tissues from the coeliac axis to the base of the bladder and prostate were cleared and 96 to 168 lymph nodes were examined in each. Two who had no nodes involved in the surgical specimen were free of metastases in the cleared postmortem preparation. Four who had metastases in the surgical specimen also had metastases in the cleared specimen. In three of these four, the involved nodes remaining after surgery could have been removed if the resection had been 1.5 cm. wider! In one, a resection of all of the inferior mesenteric artery would have been needed to remove all involved nodes. These findings reemphasize the fact that we must not limit the resection of lymph node containing tissue in carcinoma if we strive for permanent cure.

TABLE XIII

- 19 postoperative deaths
- 15 had involved nodes in surgical specimens
- 8 postmortems refused
- 3 postmortems not cleared
- 0 missed nodes
- All had involved nodes in specimens
- 8 retroperitoneal tissues cleared
- 4 no retroperitoneal metastases
- 2 with involved nodes in specimen
- 2 without involved nodes in specimen
- 4 with involved nodes remaining after surgery.

Three patients were pregnant when the carcinoma of the rectum was discovered. Two have long time cures.

TABLE XIV

PROGNOSIS IN PREGNANCY WITH CANCER OF THE RECTUM

No.	Age	% Circ. Bowel	Location	Duration Symptoms	Operation	Died	Well
1	28	65	Intraperitoneal	6 Mo.	Obst. Resection	2 yr.	
2	34	75	Extra-peritoneal	6 Mo.	Miles		9 yr.
3	38	80	Extra-peritoneal	4 Mo.	Miles		7 yr.

The first and third patients had full-term deliveries one or two months before surgery. The second patient had an abortion at four months.

New carcinomas have developed in seven of the 200 patients. In each of these cases there is a very strong evidence to suggest that these are new tumors and not metastases.

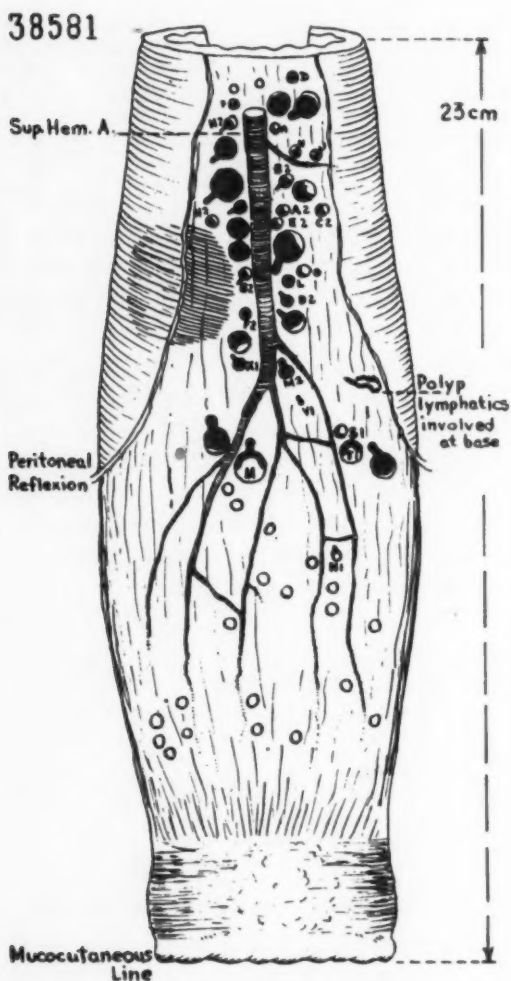


FIG. 2.—A 58-year-old man who had had symptoms for two months. The tumor was 5 cm. above the peritoneal reflection and it involved 40 per cent of the circumference of the bowel. Abdominoperineal resection was performed. The specimen contained 60 lymph nodes and 35 of these contained carcinoma metastases on microscopic section. The nodes containing carcinoma are shown in solid black. The size of nodes and the portion of each node replaced by tumor is indicated. The tails represent lymph channels filled with carcinoma. Such channels are almost never seen except where the nodes central to the involved channels are already heavily involved with carcinoma, as in this specimen. The patient had a fatal blood transfusion reaction in another hospital two months later. Post-mortem failed to show any remaining carcinoma. Retrograde metastases occurred 5 cm. below this tumor.

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TABLE XV
NEW TUMORS (EXCLUSIVE OF SKIN)

	Nodes at Operation	Polyps,	Location of New Tumor	Died	Well
1. Extraperitoneal		0	Transverse colon	7 yr.	9 yr.
2. Transverse colon		0	Rectum	3 yr.	
			Descending colon	4 yr.	5½ yr.
3. Intraperitoneal	0	0	Splenic flexure	5½ yr.	5 yr.
4. Intraperitoneal	0		Descending colon	4½ yr.	4 yr.
				10 mo.	
5. Left colon			Cecum	7 yr.	5 yr.
6. Left colon			Breast	4 yr.	4½ yr.
7. Intraperitoneal		0	Common duct	2 yr.	3 yr.

The patient with a previous resection, either with or without a colostomy, must be watched carefully or these new tumors may cause almost complete obstruction before they are discovered.

If we exclude those patients who have died of other causes without any sign of recurrent carcinoma and those who had no follow-up and those who died postoperatively, the prognosis would be:

TABLE XVI
166 CASES OF CARCINOMA OF THE COLON

	% Alive 5 Years
114 alive 5 years.....	68.7
58/89 extraperitoneal rectal.....	65.2
36/48 intraperitoneal rectal.....	75.0
9/11 right colon.....	82.8
11/18 left colon.....	61.1
54/100 with involved nodes.....	54.0
60/66 without involved nodes.....	90.9
26/53 extraperitoneal with involved nodes.....	49.1
32/36 extraperitoneal without involved nodes.....	88.8
18/30 intraperitoneal with involved nodes.....	60.0
18/18 intraperitoneal without involved nodes.....	100.0
7/9 right colon with involved nodes.....	77.7
2/2 right colon without involved nodes.....	100.0
3/8 left colon with involved nodes.....	37.5
8/10 left colon without involved nodes.....	80.0

The most striking finding here is in those tumors of the transverse colon, splenic flexure, and descending colon where there were involved nodes. All of these had obstruction resections and only three of the eight (37.5 per cent) were alive five years. The widest possible resection is indicated here rather than the usual V-shaped wedge of mesentery resected. The favorable prognosis (77.7 per cent) seen in right colon lesions having involved nodes is undoubtedly due to the wide resection of mesentery (54 nodes per specimen) performed when doing an ileotransverse colon resection and anastomosis.

CONCLUSIONS

In this study of 200 patients having resection for carcinoma of the colon, there was a 96.5 per cent five-year follow-up. One hundred and fourteen were known to be alive five to ten years (57 per cent). In the study of the surgically removed specimens, microscopic sections were made of over 10,000 different

lymph nodes, carefully plotted as to location in relation to tumor and surgical landmarks. A number of facts stand out.

The lymphatic spread of carcinoma of the colon is primarily embolic. The nodes where the emboli lodge prevent further spread until the node is completely overwhelmed by carcinoma. Further embolic spread is through the

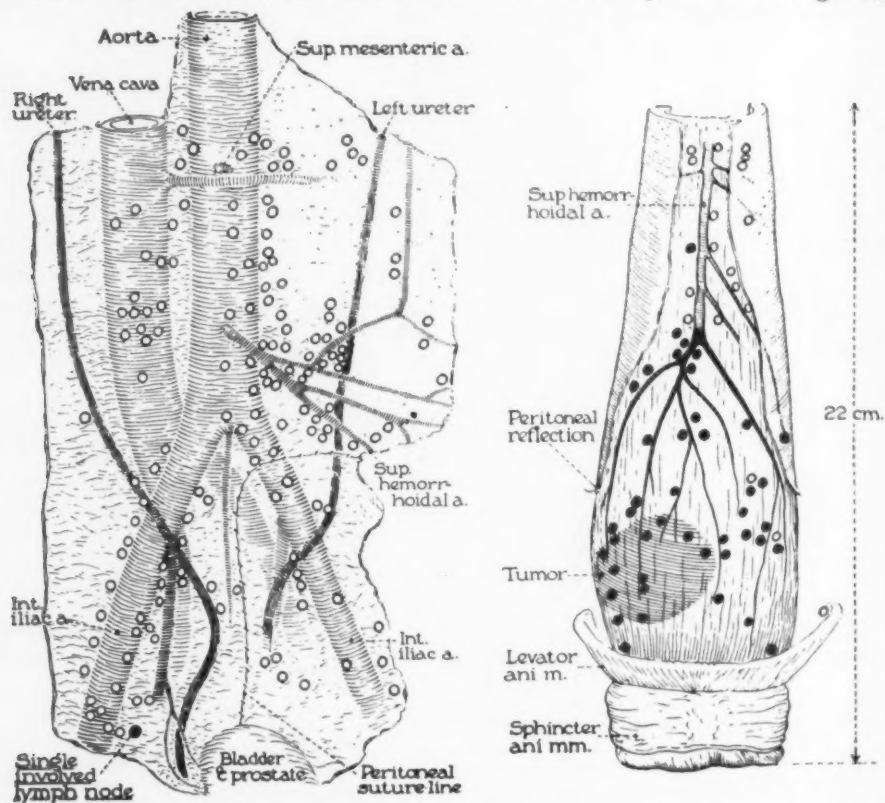


FIG. 3.—A 63-year-old man who had had symptoms for more than a year. This carcinoma was biopsied 12 months before, but he had refused operation. The tumor was ulcerating and it had penetrated all coats of the bowel. Nodes were palpable in the hollow of the sacrum. Sixty-two nodes were found in the surgical specimen; 43 of them showed metastases. He died of a pulmonary embolus on the 8th postoperative day. One hundred sixty retroperitoneal nodes were examined microscopically. In spite of the extensive lymph node involvement, there were no metastases above the point of resection. The one node involved was about 1 cm. lateral to the widest point of resection along the levator ani muscle.

collateral channels, each new node involved tending to make a longer and more difficult channel for a new embolus to travel. Spread from one node to another does not seem to be common. Thus, the finding of a group of involved nodes within the field removable by surgery does not mean that a case is hopeless. However, it does indicate the need for the widest possible resection of lymph nodes draining the area of the carcinoma.

1. In each of the regions of the bowel studied, patients in whom no lymph node metastases could be found in the surgical specimens had a five- to ten-

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year survival rate of 78.5 per cent. If those who were lost to follow-up and those who died postoperatively and of other causes after leaving the hospital were taken into account, this figure would be even more impressive (90.9 per cent).

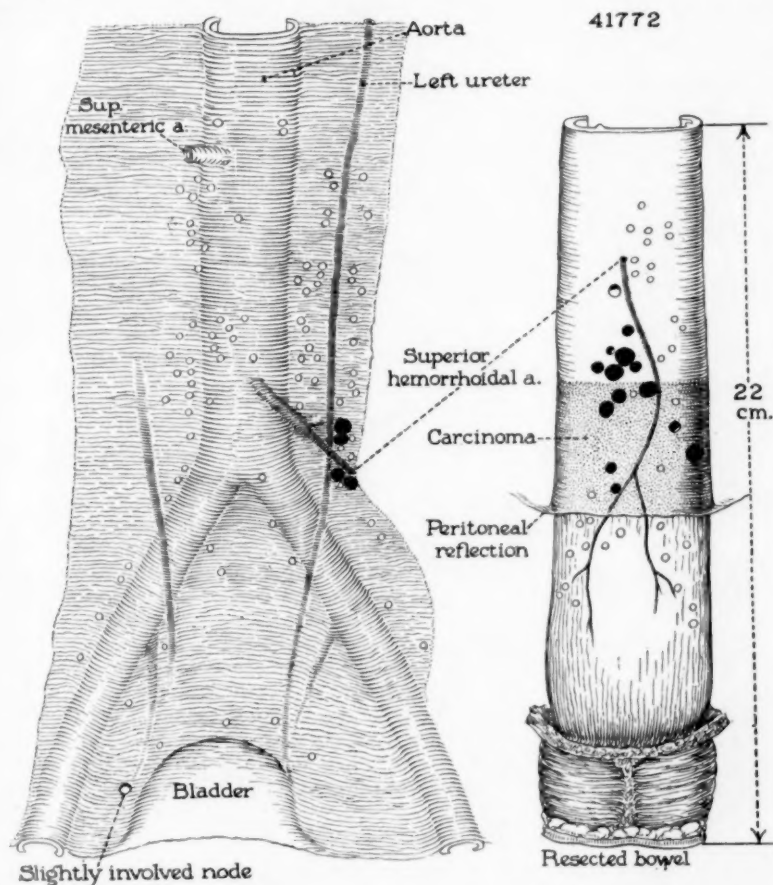


FIG. 4.—Seventy-two-year-old man who had had symptoms for four months. The surgical specimen contained 46 lymph nodes. Fourteen of these contained metastases. He died of pneumonia. The autopsy specimen contained 114 lymph nodes. Four nodes above and one node just lateral to the field of resection contained metastases. This is an example of metastasis laterally along the levator ani muscle as well as upward along the superior hemorrhoidal artery. In spite of a very large tumor, the lymphatic metastases were localized to an area which could have been resected.

2. Of the 125 having lymph node metastases, 56 lived five years (44.8 per cent). However, this varied depending on the location of the carcinoma. Those with carcinoma of the middle and left colon and of the extraperitoneal part of the rectum had a 37.5 per cent survival. Those of the right colon had a 61.5 per cent survival and those of the sigmoid and intraperitoneal part of the rectum had a 51.4 per cent survival rate. Several factors contribute to this difference. In the extraperitoneal part of the rectum, 23.2 per cent

developed local recurrence and 15.9 per cent developed liver recurrences. In the remainder of the bowel, local recurrences were not as easy to demonstrate since they do not cause symptoms early but they are obviously less frequent. If this incidence of local recurrence were disregarded, the prognosis in the extraperitoneal part of the rectum would be as good as in any other part of the colon.

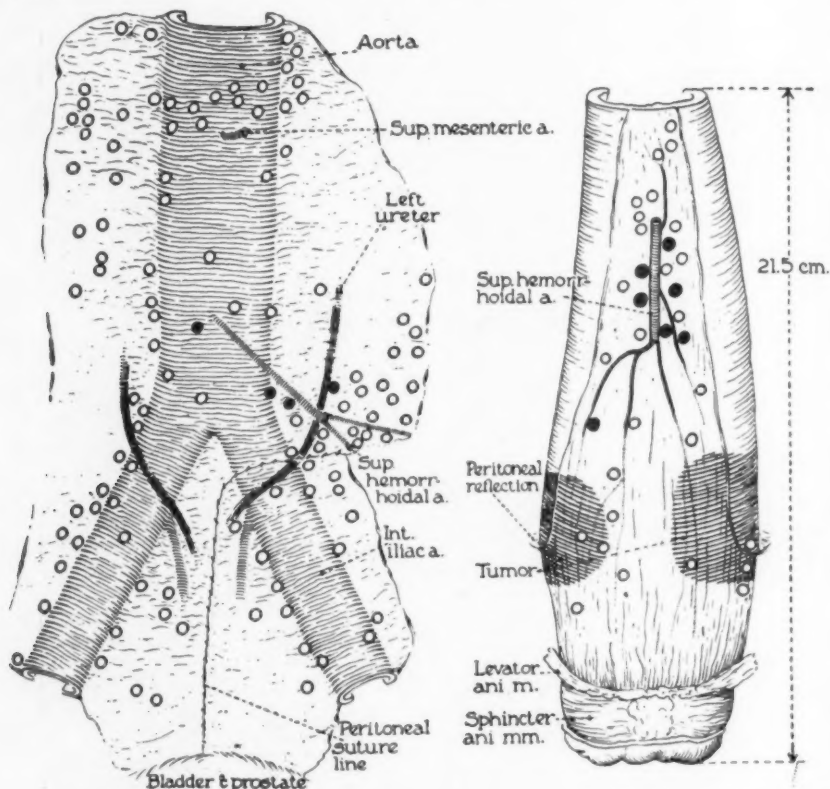


FIG. 5.—A 72-year-old man. He had had symptoms for six months. The surgical specimen contained 35 nodes and seven of these contained metastases. He died of bronchopneumonia. One hundred eleven nodes were studied in the postmortem preparation; four contained carcinoma. The highest metastasis was in a node found at the junction of the inferior mesenteric artery and aorta.

3. The 37.5 per cent survival rate of those having carcinoma of the left side of the colon when node metastases are present indicates the need for wider resection of mesentery in this area.

4. Resection of fixed tumors and the structures to which they are adherent give a better prognosis than might be expected, a 40 per cent five-year survival. Twenty per cent died postoperatively. This figure will be much improved when chemotherapy is used.

5. Retrograde metastases to nodes one to five centimeters below the tumor occurred in seven of the 153 tumors below the promontory of the sacrum (4.6 per cent).

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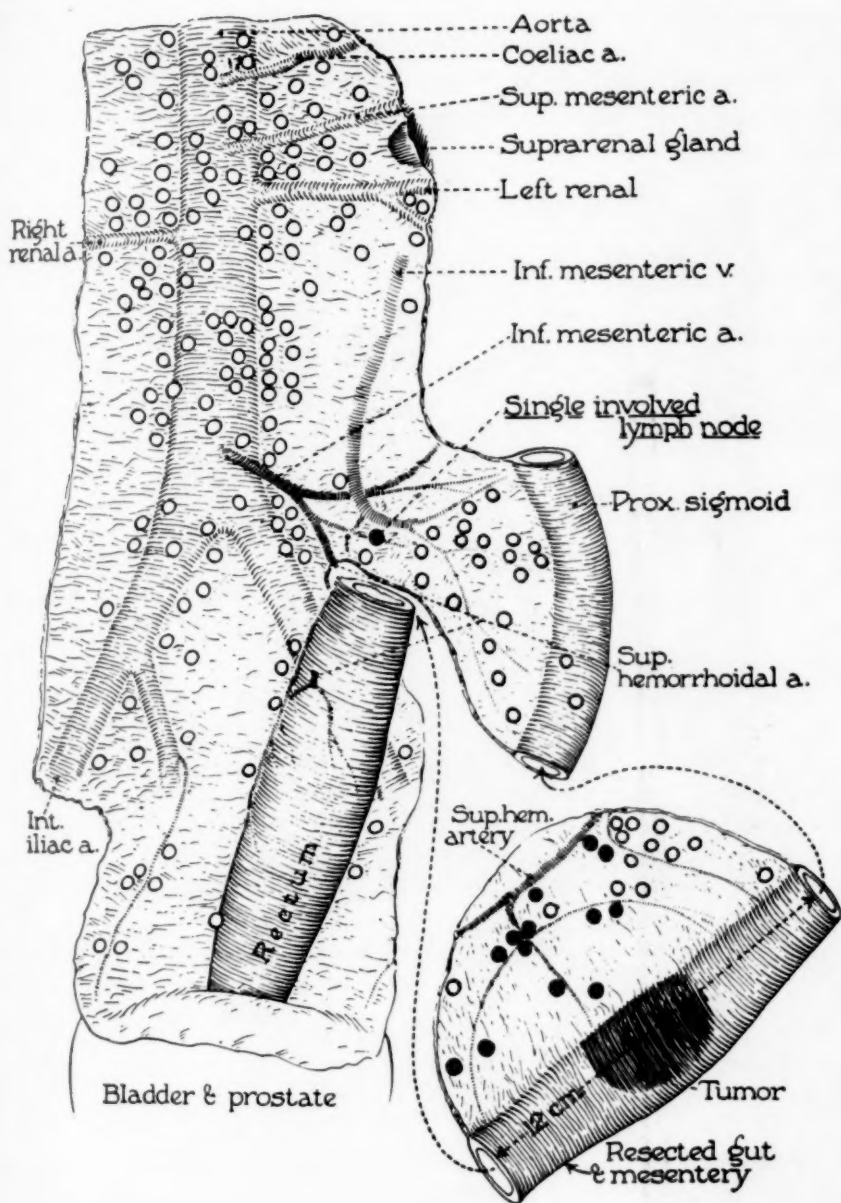


FIG. 6.—A 66-year-old fat man. He had had a known coronary thrombosis ten months before. The lesion was one inch above the peritoneal reflection. It was the size of a fist and there was a mass of nodes extending to the promontory of the sacrum. A David type of obstruction resection was performed. He died 14 days after surgery of myocardial failure. One hundred sixty-eight nodes were found in the postmortem preparation. The one involved node was less than 1 cm. beyond the line of resection.

6. The liver was the site of recurrences in 10 per cent to 15.9 per cent of the tumors. These were probably due to blood borne metastases and bear out the figure of 15 per cent blood vessel involvement reported by Coller.

7. When small "grain of sand" nodules of a uniform size are found in the liver, the operator should not give too pessimistic a prognosis as most of these are scars.

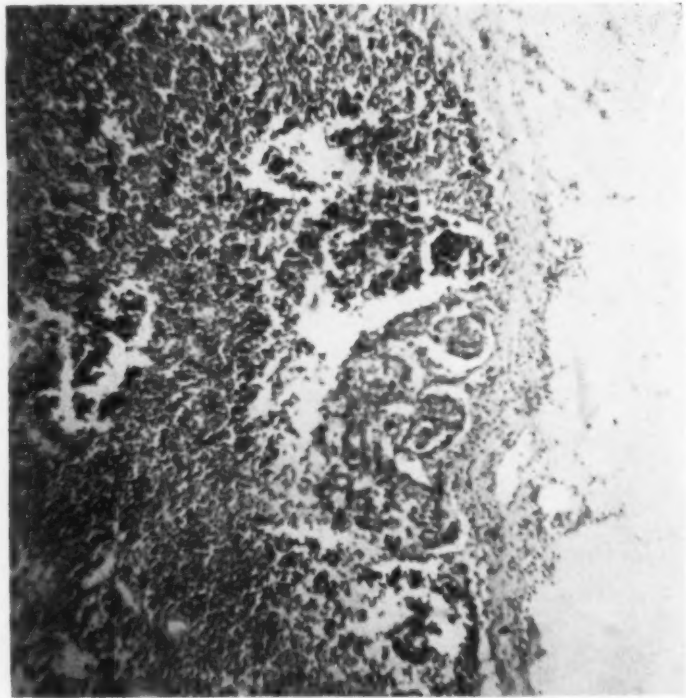


FIG. 7.—Photomicrograph of the entire amount of carcinoma metastasis found in the one node which was not removed in the surgical specimen.

8. Two of three patients who developed carcinoma of the rectum while pregnant lived over five years. This suggests that the gloomy prognosis given pregnant women with neoplasms may not be justified in carcinoma of the rectum.

9. Postmortem examination of those dying in the hospital after resection for carcinoma of the rectum showed that the ordinary postmortem examination will usually fail to demonstrate small metastases in the remaining retroperitoneal lymph nodes. Four of 11 who had postmortems were found to have metastases to nodes in the retroperitoneal tissues. In three of these, complete removal of all node metastases would have been obtained if the field of resection had been 1.5 cm. wider.

10. It is interesting to speculate on the fate of the cancer cells left in these nodes (nine) had the patient lived. In some, inflammation might have resulted

either in death of the cells or fixation in heavy fibrous tissue. It is not unlikely that such metastases in lymph nodes missed at operation finally grow. They might grow to great size without giving symptoms. We have sections of the blood vessels supplying lymph nodes being invaded by cancer. Possibly emboli from such a source might be responsible for the sudden appearance of multiple metastases many years after resection of the primary growth.

11. New carcinomas developed in seven patients who had had resections. This does not include carcinoma of the skin. In some, the diagnosis was not made for several months after symptoms appeared. Patients who have had one cancer of the colon should be reexamined carefully whenever any symptoms suggesting carcinoma appear.

12. In evaluating the type of procedure used in treating carcinoma, the survival rate is important. Of those who died of recurrence in less than five years, two-thirds occurred within three years and one-third between three and five years. Six of those listed as five-year cures developed recurrences and were dead or dying in less than seven years. In view of the appreciable percentage who develop recurrence in the fourth and fifth year after operation, it seems foolish to consider anything less than a five-year survival as a cure. Such short term survivals should not be included in discussions since they lead the general practitioner to false conclusions.

Finally, this study indicates the need for the widest possible resection in carcinoma of the colon. Lesions which are partially or completely below the peritoneal reflection have a high incidence of local and liver recurrence and pull through or sleeve resections are not much better than a local resection. The Miles operation seems to give the best chance of cure here.

As far as lesions within the peritoneal cavity are concerned, we have performed obstruction resections on several that could be palpated when doing a rectal examination. This is justified if *not only the bowel wall but the blood vessels and lymph bearing tissue* are resected at least one and a half to two inches below the lesion as well as to a point just distal to the first sigmoid artery; this is a point about one and a half to two inches above the promontory of the sacrum. If this is not done, involved nodes will be missed. The David extraperitoneal procedure will allow for such a resection in many. If, after such an extensive resection of mesentery there is still an adequate blood supply to the distal loop, we will not object to end to end anastomosis. The point of the discussion about end to end anastomosis is missed, it seems to us. It should be, "Can you remove all of the cancer?" and not, "Can you sew two ends of bowel together?" Obviously, in those intraperitoneal lesions below the promontory of the sacrum which are large or have palpably enlarged nodes, the abdominoperineal resection will give a greater chance of cure.

BIBLIOGRAPHY

- ¹ Gilchrist, R. K., and V. C. David: *ANNALS OF SURGERY*, 108, No. 4, 1938.
- ² Collier, F. A., E. B. Kay, and R. S. MacIntyre: *Surgery*, 8, 294, 1940.
- ³ David, V. C.: *S. G. & O.*, 59, 491-495, 1934.
- ⁴ Collier, F. A., and H. K. Ransom: *S. G. & O.*, 78, 304-315, 1944.

DISCUSSION.—DR. FRED W. RANKIN, Lexington, Ky.: Dr. David and Dr. Gilchrist deserve great commendation for this enormously important piece of work on the lymphatic spread of rectal cancer. It is an extension of earlier work done by them and, subsequently, corroborated by other workers in this country and abroad. No one, so far as I know, has ever done such a meticulously painstaking pathologic examination of post-operative specimens as they have, and I think that their demonstration that the more glands one examines, the more often their extension is demonstrated, is of far-reaching significance. This contribution likewise buttresses the epic work of Miles published at the turn of the century and more strongly than ever emphasizes a number of basic points dealing with the spread of cancer and directly bearing upon the type of operation indicated for eradication of rectal malignancy.

1. They show conclusively that it is essential to examine a large number of glands in any operative specimen, and they have developed a method of examination which is unique and useful. Their average of 55 glands per specimen is far above that of most pathologists.

2. They indirectly emphasize the grade of the growth as a good yardstick whereby one measures the prognosis. It has likewise been my experience that the longevity is in direct ratio to the grade of the growth and, consequently, the lower the grade, the less likely early metastasis, and the higher the grade, the more likely early metastasis.

3. They clearly demonstrate that radical extirpation of rectal malignancy with a widespread removal of gland-bearing tissue gives the highest percentage of long time freedom from recurrence. Even when there is no involvement about one-half of their patients have lived five years free from return. This fundamental fact, which has long been applied in surgery of the breast and elsewhere, is particularly applicable in surgery for rectal cancer, since the prognosis here is so obviously superior to that of cancer elsewhere in the gastrointestinal tract.

It would seem unnecessary to point out that any operation which is predicated upon any other thesis than the widespread dissection of gland-bearing areas with the growth is excessively vulnerable. In operations for cancer of the rectum my own choice has been for the past fifteen years the one-stage combined abdomino-perineal resection after the technic of Miles.

Increasingly better preparatory measures, a more thorough understanding of a balanced physiologic equilibrium, and more meticulous attention to technical details have widely extended the scope of this operation. In a recent review of 167 cases of my own done between 1934 and 1941, and whose postoperative ages therefore run from seven to 13 years, I have found 55 per cent of them alive and free from recurrence as of this date. The operative mortality in this group was 5.3 per cent and the resectability rate was 74 per cent. It is interesting to note two other cases which I have seen in my service in the last year with recurrences in the posterior vaginal wall following the Miles' operation, one of these cases done by me and one done by another member of this Association three and four years ago respectively. This evidence that there is a downward spread of lymphatics through which cancer occasionally metastasizes is definite, I think, and although it is a small group, it has a direct bearing on the prognosis. Moreover, it is generally recognized that lateral spread into the ischio-rectal fossa occurs in a really larger group of cases, and this, I think, necessitates a widespread removal of the levator muscles. Most important, however, the greatest spread of rectal cancer is upward into the mesentery of the sigmoid and these tissues may be removed radically only by some operation which includes a colostomy.

The recent rediscovery of the pull-through operation and the great emphasis placed by some surgeons on technical procedures which decry the sacrifice of the sphincteric mechanism of the rectum make it important, I think, that experienced surgeons point out again and again the limitations of such types of operations in the vast majority of cases. Technically the operation is not difficult, but that actually is hardly the important consideration. Actually, one must ask of any operation for cancer how many patients are alive following it at any given time? That is the true test of a surgical procedure. For my

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own part, I agree with David and Gilchrist that the sphincter-saving operations are little more than local excisions for all cancers situated below the peritoneum.

I had thought that the question of colostomy had been settled definitely 20 years ago, but apparently a new generation insists on a re-exploration of an already discredited field. It seems to me of utmost importance that the limits of operation be extended as widely as possible and that local attachment and metastasis do not always preclude resection, for only by radical and courageous surgery will the horizon of curability in cancer of the rectum be extended.

DR. THOMAS E. JONES, Cleveland, Ohio: I merely want to call attention to one figure in Dr. Gilchrist's statistics, namely, that 22 per cent of these cases with lesions in the ampulla had local recurrence. Miles went to this operation primarily for that reason, because of the tremendous number of local recurrences in the perineum which followed previous lesser procedures. This figure of 22 per cent would seem a little high but it proves further that radicalism is necessary and that revival of the pull-through operations and low anastomosis will be short-lived.

DR. RICHARD B. CATTELL, Boston, Mass.: This report of Drs. David and Gilchrist, together with their previous studies, has added a great deal to our knowledge of lymphatic spread of carcinoma of the colon and rectum. Their method of clearing their operative specimens for demonstration of all nodes is the most accurate method of determining the extent of lymph node involvement. It should be pointed out that this information in the individual case is not available at the time the surgeon makes the decision regarding the extent of the resection. This must be based on the operative findings.

In a review of 114 patients with carcinoma of the rectum operated upon at the Lahey Clinic in 1945, we found a preponderance of cases with extensive involvement. Only 39 had the lesion confined to its primary site. Regional nodes were involved in 24. Local extension occurred in 11, while 14 had direct invasion of other organs, not including 26 who had liver metastases. We were unable to determine by operative exploration the extent of the spread. Because of this experience we believe that abdomino-perineal resection is necessary to offer the greatest chance for cure.

In a previous study of five-year results, we found that 80 per cent were free of recurrence when there was no spread, while if lymph node involvement was found, this figure dropped to 30 per cent. If blood vessel invasion could be demonstrated, the five-year survival rate was 15 per cent.

Dr. Colcock, of our surgical staff, has recently completed a ten-year follow-up study of patients having resection for carcinoma of the rectum. When lymph nodes were not involved, 60 per cent survived five years and 51.8 per cent survived ten years, yet when lymph nodes were involved, 30.2 per cent survived five years and 23.2 per cent survived ten years.

We are confronted with the fact that the majority of patients who have cancer of the rectum have extension of their disease beyond the primary site. We must not lose sight of this fact in planning our operative procedure. The best results should follow the most radical procedure, that of abdomino-perineal resection.

DR. OWEN H. WANGENSTEEN, Minneapolis, Minn.: Inasmuch as President Churchill has asked whether there is anyone here to speak for the more conservative operation in which continuity is re-established, I come forward only in response to that request. In doing so, I admit freely that, in low-lying rectal lesions less than 6 cm. from the external anal orifice, the sphincter-saving operation should not be done. And especially in large ampullary lesions in juxtaposition to the levators, the conservative operation is out of order—a confession that I have made already elsewhere (*Surg. Gyn. & Obst.* 81:1, 1945).

You can overdo anything—even a good thing such as the abdomino-perineal operation! I have no quarrel with the thesis that, from the point of view of curing cancer of the rectum, there is no operation superior to the abdomino-perineal operation. However, it is not a light matter to deprive a man of his rectal sphincter. It is perhaps an advice

more easily given than accepted. Moreover, surgeons cannot make a sphincter and one cannot be bought in any market at any price. Continence of feces without the internal sphincter of the rectum does not exist and operations which destroy or remove the internal sphincter fail to preserve continence.

The difficulty of the matter is, we are all such poor prophets. If one could only know with assurance that he is not depriving his patient of his rectal sphincter unnecessarily or, on the other hand, that sacrifice of the rectal sphincter is mandatory to cure the cancer—if these unknowns could be resolved, then a surgeon could always choose the right operation. Dr. Gilchrist states that he has had a local recurrence incidence of 22 per cent in the abdomino-perineal operation for rectal cancer. And this, of course, is the experience of all surgeons in operating for cancer. There is no one operation that will cure all cancers. What our local recurrence incidence has been in the 60 to 70 patients upon whom we have performed the more conservative operation, we do not yet know. Despite the circumstance that I have a number of patients who are well without evidence of recurrence after excision of lesions lying 4 to 6 cm. from the anal orifice, nevertheless I have learned the bitter lesson that it is unwise to attempt to salvage the sphincters in such low-lying lesions. If one does so, he compromises on the cure of the cancer. With reference to lesions in the rectosigmoid, however, I have the impression that as satisfactory an operation for cancer can be done for lesions here with restoration of continuity as with the more radical abdomino-perineal operation.

Surgeons should be consistent, though Emerson once said that "consistency is the hobgoblin of small minds." Those who affect to believe in the wisdom of excising greater lengths of intestinal segments as well as wider excision of lymphatic areas of spread should not be advocating the exteriorization operation for cancer of the colon. My associate, David State, has recently suggested in doing the Miles operation for cancer of the rectum in patients exhibiting lymph node involvement near the origin of the inferior mesenteric artery, that the mesentery of the entire left colon be excised, establishing the colostomy in the transverse colon. In cancers of the descending colon, more often than not, I mobilize both the splenic and the sigmoid flexures and anastomose the transverse to the pelvic colon. On a few occasions, because of the extent of lymph node involvement, I have excised the right colon as well, anastomosing the ileum end-to-end to the terminal pelvic colon. I have been led to do this in seeing patients with recurrent cancer around the left ureter and even the aorta a few years after local excision of lesions in the descending colon. Certainly, such a lesion should not be treated by the exteriorization operation.

In conclusion, I would suggest that, a tempered ambition to save the rectal sphincter as well as to cure the cancer, is a praiseworthy objective in *suitable* cases of cancer of the upper rectal ampulla and most, if not all, removable cancers of the rectosigmoid.

DR. LEO ELOESSER, San Francisco, California: Just a small voice from the wilderness. I am inclined to disagree with both Dr. Gilchrist and Dr. Wangenstein on one point, viz., I think one has to consider not only how *long* one's patients are going to live, but *how* they are going to live. There is little doubt that an abdomino-perineal excision with permanent colostomy may assure a maximum percentage of freedom from recurrence in low-lying cancer of the rectum. However, I think that some of us might be inclined to forego this maximum and accept a 10 per cent or so of risk—a risk of living a few less years with a normally functioning anal sphincter, instead of eking out a few more years of life embarrassed by colostomy.

DR. R. KENNEDY GILCHRIST, Chicago, Ill. (closing): The most interesting fact in this study has been the percentage who had five-year survival even in the days before chemotherapy. As our studies progressed, we have become more and more radical in our resection of the lymphatics draining the carcinoma, and I feel certain that a study of those cases done in the last five years will show an even more favorable percentage of five-year cures.

ADJUVANTS TO SURGICAL THERAPY IN LARGE BOWEL MALIGNANCY*

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THE TREATMENT OF MALIGNANT LESIONS of the large bowel presents a multitude of problems about which there is no unanimity of opinion. Surgeons are not agreed on what constitutes operability; whether radical operation should be done in the presence of major metastases; the advantages of a one-stage over a two-stage operation; aseptic versus open anastomosis, or various modifications of the Mikulicz operation versus end-to-end or end-to-side anastomosis.

The well known caution of our profession has often led us to be slow in adopting concepts and procedures which may have much to commend them. Brunschwig¹ has recently summarized the concept of radical surgery as follows: "The advocacy of a more radical surgical attitude in regard to advanced abdominal cancer is not to be interpreted as justification for indiscriminate radical operations. In appreciably extending radical surgery, proper selection of patients is of utmost importance. By persistent and concerted efforts in these directions, surgeons will contribute in their field to the general advance in the cancer problem." With this statement we agree. With its acceptance many lesions which have previously been considered inoperable become operable.

The answer to many of the problems which confront the surgeon interested in malignancy of the colon is not to be found in statistical analysis alone, however useful this tool may be when used within its limitations. Operability will vary with the skill and boldness of the surgeon; the method of operation frequently varies with training and experience. Both may be influenced by attention focused upon the immediate mortality rather than upon the five and ten year cures, however few they may be.

We propose to present a few adjuvants to surgical therapy which we and others have found to be useful.

ANEMIA AND HYPOPROTEINEMIA

Anemia is frequently observed in association with neoplasms of the large bowel. It is seen in the most advanced type in certain instances of large bowel polyposis and in cancer of the cecum and ascending colon. In the latter site it may be so severe as to simulate pernicious anemia.

Many of these patients are also in poor nutritional condition, a circum-

* Read before the American Surgical Association, March 25, 1947, Hot Springs, Va.

stance brought about by an inadequate intake of foodstuffs and at times by an exorbitant loss of protein in the stool during periods of diarrhea. Thus malnutrition and anemia are often found to exist in the same patient (Fig. 1).

When hypoproteinemia and anemia are present, the circumstance is a complex one. George Whipple² has described this state as follows: "We believed that in a dog, both anemic and plasma depleted, we could influence the protein flow toward hemoglobin by one food factor or toward plasma protein by another food. . . . To our surprise we observed that such dogs

===== Anemia and Hypoproteinemia =====

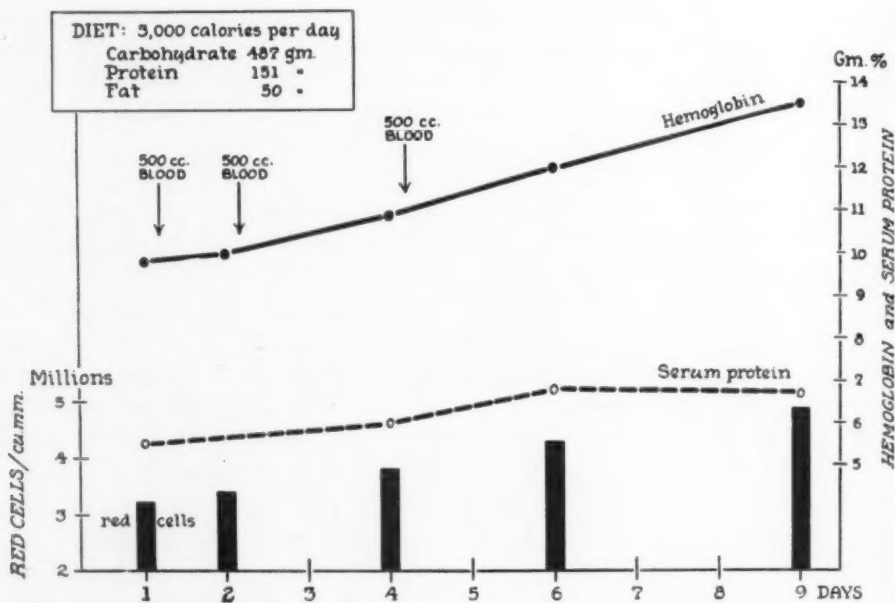


FIG. 1.—Coexisting anemia and hypoproteinemia corrected by transfusions and diet.

(hemoglobin and plasma protein deficient) always produce more hemoglobin than plasma protein no matter what diet protein is used. . . . Hemoglobin in its production may draw on the plasma protein but hemoglobin stands apart in the protein economy and does not contribute freely to the protein pool. The body guards jealously the fabrication of hemoglobin and given a real need for both plasma protein and hemoglobin the protein flow favors hemoglobin, which under these circumstances is produced in more abundance than the plasma protein."

Every possible effort should be made to correct an existing anemia in protein deficient patients in whom attempts are being made to correct the protein deficiency. Patients presenting both anemia and hypoproteinemia should be transfused vigorously prior to operation. This was repeatedly demonstrated in patients during World War II. Dependence for the correction of the nutritional defect could not be placed on diet, minerals or small

transfusions, for even under these circumstances the protein and minerals ingested went first to provide the components necessary for the synthesis of hemoglobin and not to replace the depleted stores of body and plasma protein.

We³ have shown, as have others, that the hypoproteinemic dog is more susceptible to hemorrhagic shock than is the normally nourished dog, and no one would question the increased susceptibility of the undernourished patient to traumatic or hemorrhagic shock (Fig. 2). The anemic patient is likewise

**The Loss of Blood Necessary to Reduce the
Blood Pressure below 60 mm. Mercury
for Thirty Minutes**

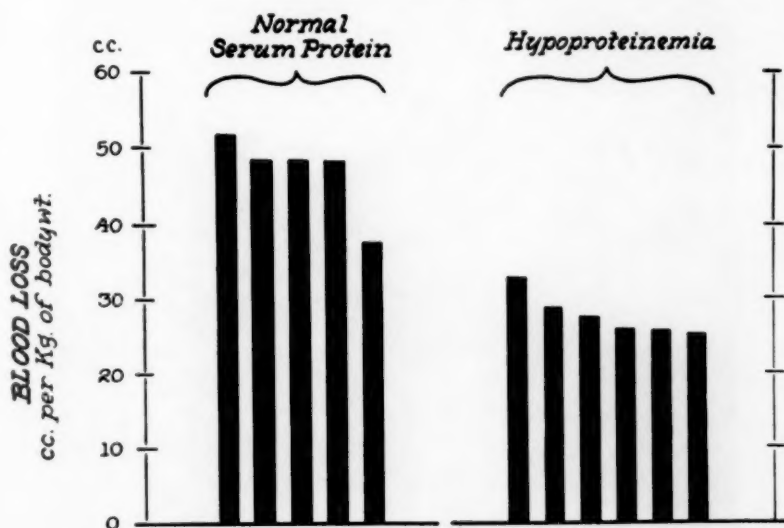


FIG. 2.—The loss of blood necessary to reduce the blood pressure below 60.0 mm. of mercury for 30 minutes in hypoproteinemic dogs and dogs with normal serum protein levels.

more susceptible to shock from trauma or blood loss. Furthermore, the nutritionally deficient patient is more susceptible to faulty wound healing, wound infection, and exaggerated edema following trauma at sites of anastomosis. In protein deficient patients improved protein nutrition has been shown by Cannon⁴ to increase antibody formation and the production of phagocytes, thus strengthening two biologic factors which assist in the control of invasive infection. Cannon and his associates⁵ have called attention to the fact that in severe inanition the cellular tissues which supply phagocytes in large numbers undergo atrophy.

VITAMINS

Thiamin, niacin and riboflavin are concerned with the intermediate metabolism of carbohydrate^{6, 7, 8} and riboflavin is also concerned with the utilization of amino acids.⁹

The more or less general adoption of oral chemotherapy prior to bowel resection has been most helpful, but is attended by some risks unless the collateral effects of such therapy are more generally understood.

The drugs of the sulfonamide class, when given orally, demand an increase in the intake of certain vitamins. Sulfasuxidine is now widely used in the preparation of patients for resection of the colon, but it must always be remembered that within four to six days after such therapy is begun the thiamin



FIG. 3.—Miller-Abbott tube passed through the small intestine prior to resection of the colon.

output in the feces will reach a zero level unless the thiamin intake in the diet is greatly augmented.⁹

The physiologic requirements of certain vitamins are met in large part by the absorption of vitamins synthesized in the bowel as the result of bacterial metabolism.¹⁰ The chemotherapeutic agent, be it a sulfonamide or an antibiotic, reduces to a variable degree the bacterial growth, but the effectiveness in such action is attended with a reduction in the intestinal vitamin synthesis. Oral sulfonamide therapy may result in a definite reduction in the synthesis of vitamin K in the intestine with a resulting hypoprothrombinemia^{11, 12} and

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hemorrhage at the suture line. Oral streptomycin therapy would similarly effect the bacterial synthesis of vitamin K.

LONG TUBE DECOMPRESSION

In 1940 William Osler Abbott and one of us¹³ reported our early experience on the use of the Miller-Abbott tube as a means of facilitating a one stage resection and anastomosis of the right colon (Fig. 3). The method has also been favorably reported upon by Allen Whipple¹⁴ and by Newton and Blodgett.¹⁵ Our experience with its use in resections of the right colon was so satisfactory that two stage resections of the right colon have not been done in our clinic since 1938.

We have since extended its use to the preparation of patients with lesions in the more distal segments of the large bowel. The tube does not always go through the ileocecal valve but it frequently does, and in our hands at least has frequently obviated the necessity of a proximal colostomy, except where acute obstruction or marked chronic obstruction was present.

The tube is passed 48 hours before the contemplated operation, and its position is checked at intervals by fluoroscopic study. Feeding and chemotherapy are continued during this period. The tube remains in the bowel after operation until the patient's intestinal functions have returned to normal. Its use in our hands has contributed to a reduction in the over-all mortality.

CHEMOTHERAPY

The use of oral sulfonamides, especially sulfasuxidine and sulfathalidine, in the pre-operative period prior to bowel resection is now more or less generally accepted. These drugs have been useful in reducing the total bacterial population, but their action on the intestinal bacteria is highly selective and in the occasional patient the usual, or even larger, doses are without any marked effect.

More recently we have used streptomycin in these patients. This antibiotic is effective, in part at least, against all of the common intestinal pathogens. When given by mouth in a dosage of 0.25 Gm. every six hours the feces are

TABLE I
EFFECT OF STREPTOMYCIN AND SUCCINYL-SULFATHIAZOLE
ON THE NUMBER OF B. COLI PER GRAM OF FECES

Agent	Before	After 8 Days	After 8 Days in 85% of Patients
Streptomycin.....	74,836,060,000	418,000	262
Succinylsulfathiazole.....	23,700,000,000	150,000,000	98,857

free of the *Streptococcus fecalis* in eight days, and there results a marked reduction in the coliform group and the anaerobic organisms of the Welchii type (Tables I, II and III and Figures 4 and 5). We are now studying the effect of 5.0 Gm. daily to determine whether bacterial control is achieved in a shorter period of time.

In nearly every one of the earlier reported series of resections of the colon, the mortality from peritonitis was approximately 50 per cent. Chemotherapy by any method now known does not provide sterilization of the feces, but it usually does produce a marked reduction in the bacterial count of the pathogens.

In the immediate postoperative period we have administered penicillin

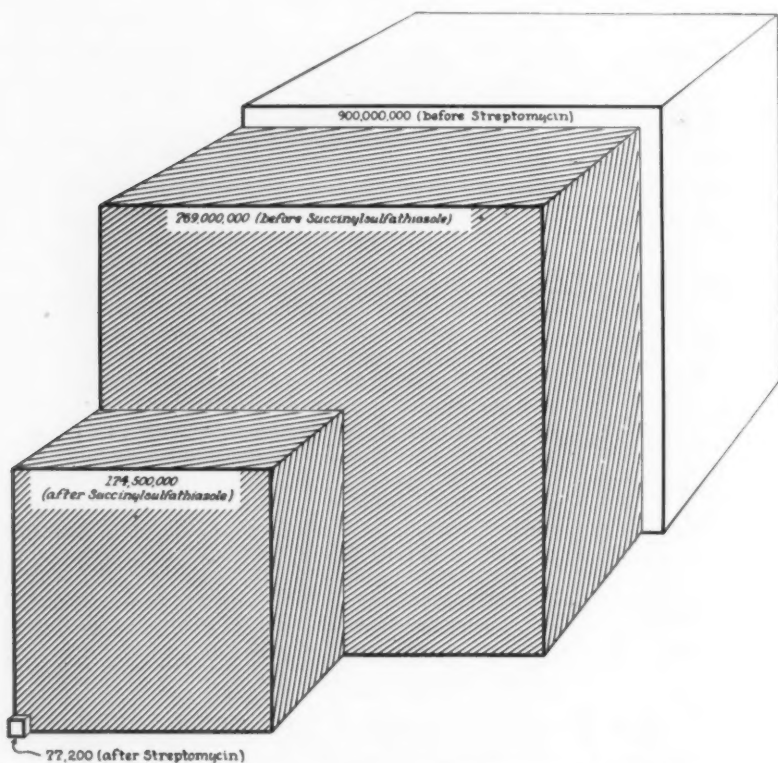


FIG. 4.—Relative effect of streptomycin and succinylsulfathiazole on the number of *Streptococcus fecalis* organisms per gram of feces.

and streptomycin in a further effort to prevent serious peritonitis. Data soon to be reported by Zinsser and Zintel¹⁶ have shown these two antibiotics to be useful in preventing spreading peritonitis following peritoneal soiling.

DISCUSSION

Even though a clean bowel and an empty bowel was not obtained by the adjuvants described in this paper, minor fecal contamination of the peritoneum at operation did not prove serious and peritonitis has not been the cause of a single death in the year 1946 during which time 53 colon resections were done, 40 in one stage (Table IV). Eighteen of the latter were performed by the open method. Prior to the adoption of the complete program as

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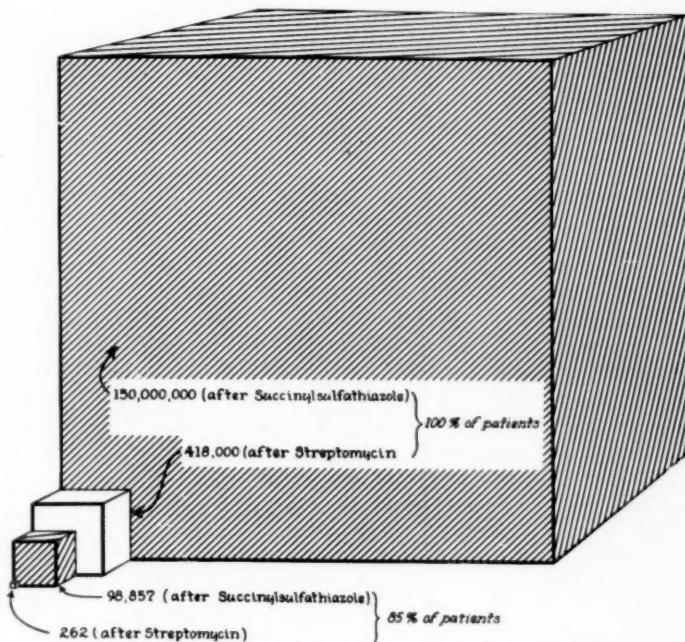


FIG. 5.—Relative effect of streptomycin and succinylsulfathiazole on the number of *B. coli* organisms in the feces as observed in all of the patients and in the 85 per cent of the patients who had the best results.

COLON SURGERY Operative Mortality by Years

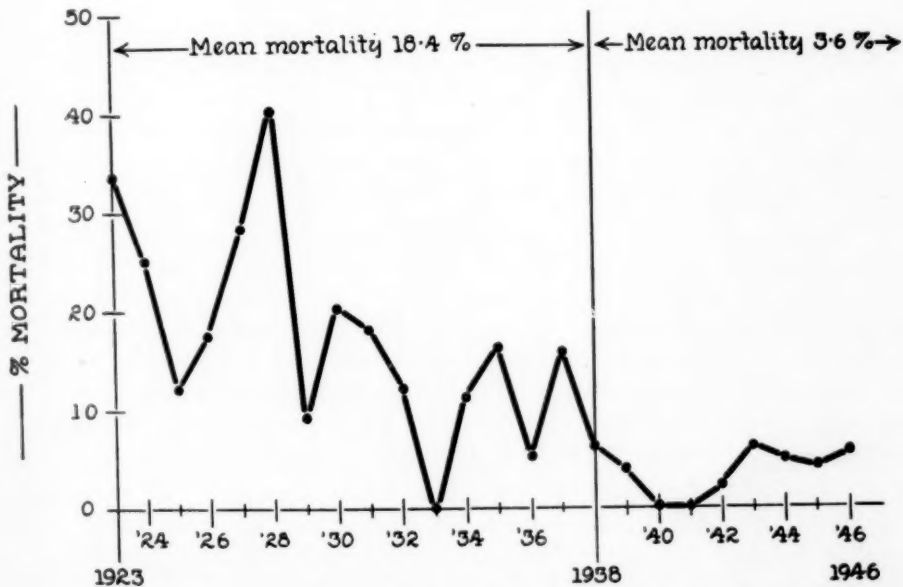


FIG. 6.—Operative mortality by years of all operations on the colon.

described total resectability for colon cancer was 64.5 per cent. During the year 1946 total resectability was 73.6 per cent. The mean operative mortality for all operations on the colon, including perforation and obstruction, from 1923 to 1938 was 18.4 per cent; and since 1938 when we began the use of a definite portion of the program, the mean mortality has been 3.6 per cent

TABLE II

EFFECT OF STREPTOMYCIN AND SUCCINYLSTREPTOGRAMIN ON THE
NUMBER OF STREPTOCOCCI FECALIS PER GRAM OF FECES

Agent	Before	After 8 Days	After 8 Days in 85% of Patients
Streptomycin	900,500,000	77,200	0
Succinylstreptogramin	769,000,000	174,500,000	141,157,833

TABLE III

EFFECT OF STREPTOMYCIN AND SUCCINYLSTREPTOGRAMIN ON THE
NUMBER OF CLOSTRIDIAL ORGANISMS PER GRAM OF FECES

Agent	Before	After 8 Days	After 8 Days in 85% of Patients
Streptomycin	33,030,000	539,900	200
Succinylstreptogramin	15,090,000	1,047,000	71,218

TABLE IV

MALIGNANT LESIONS OF THE COLON
JANUARY 1, 1946 TO DECEMBER 31, 1946

Resections of the colon	53	
One stage	40	(74.1%)
Open anastomosis	18	(33.96%)
Mortality entire group	3.8%	
One death, open anastomosis		

(Table IV). In only two years prior to 1938 was the mortality ever as low as it has been in any year since 1938.

Resection with end-to-end anastomosis is supplanting Mikulicz types of resection in our clinic. One-stage procedures have entirely supplanted multi-stage operations except in the presence of perforation or obstruction.

Nothing we have mentioned replaces the gentle handling of the bowel, the greatest care in the conservation of blood supply, the prevention of major soiling and the careful approximation of the bowel edges. But when all of these have been done, a number of patients will lose their lives from peritonitis from one cause or another. The adjuvants here reported have permitted a larger number of one stage in place of multistage operations reducing the risk of secondary anesthetization, and they have led to a more rapid recovery and a shorter period of disability and hospitalization in a larger number of patients. They have led to a substantial reduction in the mortality following operations on the colon and have, we believe, played an important part in the very marked reduction in the incidence of fatal peritonitis following resection of the large bowel.

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BIBLIOGRAPHY

- ¹ Brunschwig, A.: Radical Surgery in Advanced Abdominal Cancer, Univ. of Chicago Press, Chicago, Ill., 1947.
- ² Whipple, G.: Am. J. M. Sc., **203**, 477, 1942.
- ³ Ravdin, I. S., H. G. McNamee, J. H. Kamholz, and J. E. Rhoads: Arch. Surg., **48**, 491, 1944.
- ⁴ Cannon, R. P.: J. A. M. A., **128**, 360, 1945.
- ⁵ Cannon, R. P., W. E. Chase, and R. W. Wissler: J. Immunol., **47**, 133, 1943.
- ⁶ Peters, R. A.: Biochem. J., **30**, 2206, 1936.
- ⁷ Warburg, O., and W. Christian: Biochem. Zeit., **266**, 377, 1933.
- ⁸ Euler, H. V., H. Albers, and F. Schlenk: Zeit. Physiol. Chem., **235**, 1, 1935.
- ⁹ Najjar, V. A., and L. E. Holt, Jr.: J. Am. Med. Assoc., **123**, 683, 1943.
- ¹⁰ Burkholder, P. R., and I. McVeigh: Proc. Nat. Acad. Sc., **28**, 285, 1942.
- ¹¹ Black, S., R. S. Overman, C. A. Elvehjem, and K. P. Link: J. Biol. Chem., **145**, 137, 1942.
- ¹² Kornberg, A., F. S. Daft, and W. H. Sebrell: Public Health Reports, **59**, 832, 1944.
- ¹³ Ravdin, I. S., and W. O. Abbott: The Use of the Miller-Abbott Tube in Facilitating One-stage Resection of the Small and Large Bowel. Clinics, **1**, 179, 1940.
- ¹⁴ Whipple, A. O.: Surg., **8**, 289, 1940.
- ¹⁵ Newton, F. C., and J. B. Blodgett: Surg., **18**, 200, 1945.
- ¹⁶ Zinsser, Hans H., and H. A. Zintel: Personal communication.

OBSERVATIONS ON MORTALITY FROM ACUTE APPENDICITIS AT A UNIVERSITY HOSPITAL, 1916 TO 1946*

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THE PRESENT STUDY OF ACUTE APPENDICITIS mortality at Presbyterian Hospital, New York, is a continuation of a previous report,⁴⁵ and now comprises a 30-year period. The fact that 1946 marked the 60th anniversary of the first successful appendicectomy performed in this country (Richard Hall²⁰ at Roosevelt Hospital, N. Y., on May 8, 1886) made it seem timely to give pause and review our own results in the treatment of this surgical disease. In addition, such a study serves as a good yardstick in evaluating the work and ability of a large hospital staff. Since 1936 our records also include all cases of acute appendicitis at Babies Hospital, together with those that occasionally develop in Sloane Hospital for Women, the Squier Urological Clinic, and the Neurological Institute.

During this span of years there have been many attending staff members, interns, house surgeons, fellows, residents and assistant residents. For this reason, the results and remarks, herewith presented, are not comparable to those of individual series, or of small groups of well trained, experienced, skillful surgeons.

It is proposed to present our mortality charts with appropriate comments, together with a brief discussion of the fatalities in each subgroup during the last five-year period (war years), to make a few general remarks, to offer some practical suggestions in operative therapy, and finally to submit a plan for further reduction of appendicitis mortality, at this institution.

The classification of our cases has followed the nomenclature in our previous report so as to lend continuity to the present study and therefore the descriptive pathology of each subgroup need not be repeated here. With few exceptions,** the basis of our classification rests chiefly on the gross operative findings. This is quite important, because, if, for instance, a patient discloses an acute local peritonitis at operation, and subsequently dies of a generalized fibrinopurulent peritonitis, the death is placed in the former category where it will arouse greater attention and scrutiny. It is useful, too, in evaluating and interpreting end results. Classification of acute appendicitis on a time basis seems unsatisfactory because this disease does not progress at a steady even pace.

Many large clinics and hospitals follow a classification of their own choosing so that it is quite difficult to make relevant comparisons. Sometimes the use of the same descriptive term will reveal considerable differences in the

* Read before the American Surgical Association, March 25, 1947, Hot Springs, Va.

** A few deaths are included in this series where patients were so moribund that operation was entirely out of the question.

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interpretation of the pathology applied to it. Comparative figures, therefore, have not been extensively employed in this report.

The accuracy of any classification, dealing with acute appendicitis is open to criticism, and the reader may justly challenge the correctness of our findings. There are at least three factors of error. In the first place, many observers have pointed out that a classification, such as ours, is not feasible if the operation is properly executed. Secondly, there are many instances of transition from one pathologic subgroup to a succeeding one, so that a surgeon

FIG. 1

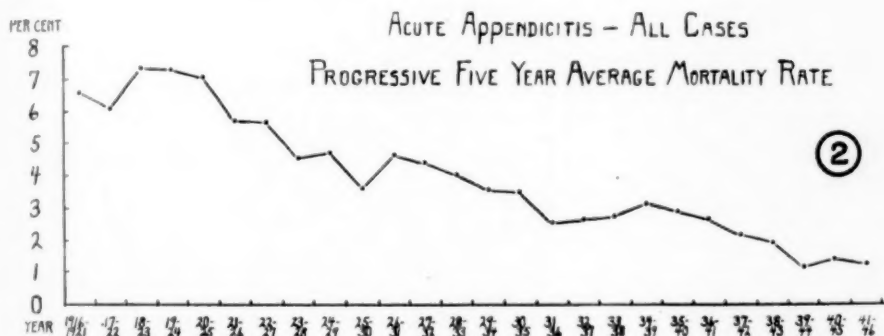
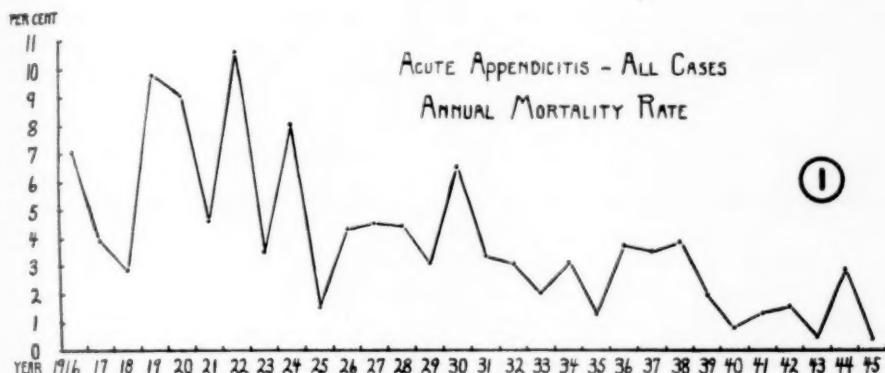


FIG. 2

FIG. 1.—Graph showing total annual death rate from 1916 to 1945, inclusive, in 5405 cases of acute appendicitis with its associated lesions. Total number of deaths: 193; total mortality rate, 3.55 per cent. Mortality rate for 1945 was 0.43 per cent.

FIG. 2.—Graph for comparison with that in Figure 1, showing the total progressive five-year average death rate from 1916 to 1945, inclusive, for all cases of acute appendicitis with its associated lesions. Mortality rate for 1941 to 1946 was 1.37 per cent.

might assign a given case to subgroup A, whilst another operator, confronted with similar findings, might place it in subgroup B. Lastly, each case history is subject to interpretation and classification by the present writer, although, in doubtful instances, an effort is made to consult the operating surgeon. It is

acknowledged, therefore, that the various subgroups may be slightly inaccurate. Nevertheless, the total mortality figures (the sum of all subgroups) can be accepted as reasonably accurate.

Not only will the annual mortality curves be shown, but the corresponding progressive five-year averages in addition. The latter are considered important because they eliminate the factor of annual fluctuation, thus providing a measure of predictability and an indication of certain trends.

ACUTE APPENDICITIS AND ITS ASSOCIATED LESIONS: ALL CASES

From 1916 to 1946 there were 5,405 cases of which 193 died. The total death rate was 3.55 per cent. The annual death rate (Fig. 1) shows considerable fluctuation but there is a definite downward trend, with 1945 showing

TABLE I

TOTAL MORTALITY RATES ALL CASES OF ACUTE APPENDICITIS AND ASSOCIATED LESIONS, REPORTED IN LITERATURE

Year of Publication	Author	Place	Period Studied	No. of Cases	Mortality per cent
1938	Ray ⁴¹	New York Hospital, N. Y.	1932-1937	886	2.1
1938	Turner ³⁷	London Hospital and Royal Victoria Hospital, Newcastle-on-Tyne	1933-1937	7329	4.07
1939	Smith ⁴⁸	St. Luke's Hospital, N. Y.	1929-1937	793	3.2
1940	Bower ⁶	Philadelphia Hospitals, Pa.	1928-1937	22,873	4.15
1940	Morse and Rader ³²	Jewish Hospital, Brooklyn, N. Y.	1915-1934	8727	2.15
1940	Reid and Montanus ⁴²	Cincinnati General Hospital, Ohio	1934-1938	921	5.97
1940	Stafford and Sprong ⁵²	Johns Hopkins Hospital, Md.	1931-1939	1317	3.6
1940	Young ¹⁹	Anderson City Hospital, South Carolina	1923-1939	3611	3.04
1941	Aud ³	Nine Louisville Hospitals, Kentucky	1939	1161	3.9
1941	Boyce and Nelson ⁸	Charity Hospital, La.	1930-1941	4963	5.1
1941	Nassau, Lorry and Pulaski ³⁷	Frankford Hospital, Pa.	1904-1939	3450	4.2
1941	Rumbold ⁴⁴	Genesee Hospital, N. Y.	1925-1939	2013	3.3
1942	Cutler and Hoerr ¹⁵	Peter Bent Brigham Hospital, Mass.	1913-1940	2192	4.4
1942	Jennings, Burger and Jacobi ²⁴	Beth El Hospital, Brooklyn, N. Y.	1930-1938	1680	1.9
1942	Rogers and Faxon ⁴⁹	Mass. General Hospital, Mass.	1929-1940	3301	3.06
1942	Slattery and Hinton ⁴⁹	Bellevue Hospital (IV Div.), N. Y.	1928-1939	677	5.1
1943	Hathaway and Watkins ²²	Cleveland Survey, Ohio	1930-1942	19,401	4.8
1945	Aycock and Farris ³	Baltimore City Hospitals, Md.	1935-1944	1151	3.0
1945	Mueller ³³	Roosevelt Hospital, N. Y.	1935-1944	1481	1.6
1946	Tashiro and Zininger ⁵⁴	Cincinnati General Hospital, Ohio	1939-1943	865	3.46

the lowest rate of 0.43 per cent. There was only one death in 1943 and 1945. In the progressive five-year average curve (Fig. 2) the diminution in mortality rate is clearly shown and, during the last five year period, the rate was 1.37 per cent.

These figures compare rather favorably with those reported in other teaching centers, or hospitals with large staffs, and a few of them are listed in Table I.

SAMPLE ACUTE APPENDICITIS

Slightly over half our total number belong in this category (2,855 cases) and, perhaps in time, we may eventually witness the vast majority of cases

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classified here. There were 14 deaths resulting in a fatality rate of 0.49 per cent. Figure 3 shows the annual mortality rate, and it will be noted that it has been zero during the past six years except for 1944 which discloses the highest annual rate in the period under study, being slightly greater than those recorded in 1920, 1922 and 1924. There were three deaths in 1944. The progressive five-year average is shown in Figure 4 and reveals a fairly uniform curve. For the past five years the rate was 0.39 per cent. Comparable results in other institutions are listed in Table II.

During the latest five-year period there were three deaths in this group, all occurring in 1944. All three were obese and elderly (69, 73 and 76 years of age). The histories were fairly typical and of short duration, but one was

TABLE II
MORTALITY RATES FROM SIMPLE ACUTE APPENDICITIS, REPORTED IN LITERATURE

Year of Publication	Author	Place	Period Studied	No. of Cases	Mortality per cent
1940	Barrow and Ochsner ⁴	Charity Hospital, La.	1937-1938	860	0.8
1940	Muller ¹³	Iltanau, Jefferson and Misericordia Hospitals, Pa.	1937-1938	259	0.0
1940	Stafford and Sprong ³²	Johns Hopkins Hospital, Md.	1931-1939	838	0.0
1941	Burke and Kuhn ¹⁰	Municipal Hospital, Buffalo, N. Y.	1935-1946	320	0.58
1941	Haggard and Kirtley ¹⁹	Haggard Clinic, Tenn.	1915-1938	2007	0.54
1941	Nassau, Lorry and Pulaski ¹⁷	Frankford Hospital, Pa.	1904-1939	1800	0.44
1941	Rumbold ⁴⁴	Genesee Hospital, N. Y.	1925-1939	1499	0.6
1942	Cutler and Hoerr ¹⁵	Peter Bent Brigham Hospital, Mass.,	1913-1940	1605	1.2
1942	Rogers and Faxon ⁴³	Mass. General Hospital, Mass.	1929-1940	2630	0.53
1942	Slattery and Hinton ⁴⁰	Bellevue Hospital (IV Div.), N. Y. C.	1928-1939	474	1.6
1945	Aycock and Farris ³	Baltimore City Hospitals, Md.	1935-1944	895	0.0
1946	Meyer, Requarth and Kozoll ³¹	Cook County Hospital, Ill.	1944-1945	281	0.78

observed for 48 hours on the medical service, having been admitted ten days previously for hypertension and cardiac insufficiency. The McBurney incision was used in all, and technical difficulties were encountered in one because of a high cecum. All were drained and sulfanilamide was applied locally in two. One patient expired the following day from cardiac failure, pulmonary edema and pneumonia. Another died on the tenth postoperative day from pulmonary infarct and pneumonia, in spite of early ambulation. The third death came on the 14th day, from progressive heart failure and pneumonia. The important contributory factors in this group of deaths were age, obesity and severe cardiovascular and respiratory disturbances. One patient presented a somewhat atypical history and technical difficulties at operation were encountered in another. The appendiceal disease was certainly not the direct cause of death although it was undoubtedly the inciting one.

ACUTE APPENDICITIS WITH ACUTE LOCAL PERITONITIS

In this group we find almost one quarter (23 per cent) of the total number of our series. There were 26 deaths in the 1,262 recorded cases, resulting in a mortality rate of 2.06 per cent—four times greater than the previous group.

FIG. 3

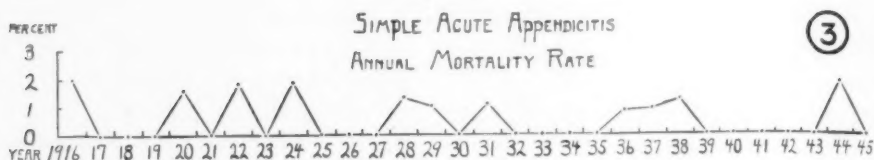


FIG. 4

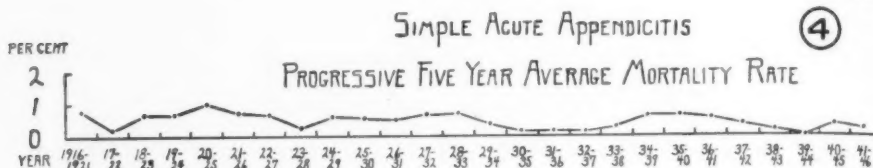


FIG. 5

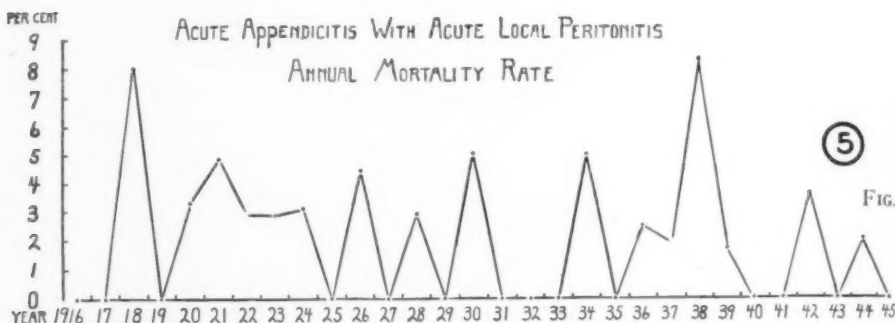


FIG. 6

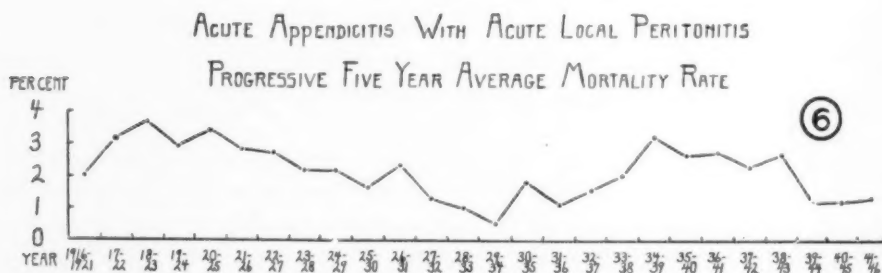


FIG. 3.—Graph showing annual death rate from 1916 to 1945, inclusive, in 2855 cases of simple acute appendicitis. Total number of deaths: 14. Mortality rate, 0.49 per cent. No deaths in 1945.

FIG. 4.—Graph for comparison with that in Figure 3, showing the progressive five-year average death rate from 1916 to 1945, inclusive, in all cases of simple acute appendicitis. Mortality rate for 1941 to 1946 was 0.39 per cent.

FIG. 5.—Graph showing the annual death rate from 1916 to 1945, inclusive, in 1262 cases of acute appendicitis with acute local peritonitis. Total number of deaths: 26; mortality rate, 2.06 per cent. No deaths in 1945.

FIG. 6.—Graph for comparison with that in Figure 5, showing the progressive five-year average death rate from 1916 to 1945, inclusive, in all cases of acute appendicitis with acute local peritonitis. Mortality rate for 1941 to 1946 was 1.35 per cent.

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The annual death rate fluctuated from 8 per cent to zero (Fig. 5) and the last five-year period carried a 1.35 per cent mortality rate (Fig. 6). The progressive five-year average shows but little improvement although there was a rather steady decline from the 1916-1921 to the 1929-1934 periods. Since then the curve has shown a serious upward trend and, although the last three periods are not as high as the preceding ones, nevertheless they reveal a slight increase. We are disturbed by these findings, and in examining the records, some of the reasons can be found. The seriousness of the true pathology was often misjudged. There were errors in operative technique. In numerous instances the operator was uncertain whether to drain, or not, and it was obvious he was confused by such pernicious catch phrases as "when in

TABLE III

MORTALITY RATES FROM ACUTE APPENDICITIS WITH ACUTE LOCAL PERITONITIS, REPORTED IN LITERATURE

Year of Publication	Author	Place	Period Studied	No. of Cases	Mortality per cent
1940	Muller ²⁵	Lankenau, Jefferson and Misericordia Hospitals, Pa.	1937-1938	78	1.3
1941	Burke and Kuhn ¹⁸	Municipal Hospital, Buffalo, New York	1935-1940	44	11.3
1941	Bohmansson and Norup ¹	Orebro Hospital, Sweden	1929-1940	416	11.0
1941	Nassau, Lorry and Pulaski ¹⁷	Frankford Hospital, Pa.	1904-1939	1159	3.5
1941	Rumbold ⁴⁴	Genesee Hospital, N. Y.	1925-1939	239	7.1
1942	Slattery and Hinton ⁴⁵	Bellevue Hospital (IV Div.), N. Y. C.	1928-1939	67	5.9
1945	Aycock and Farris ²	Baltimore City Hospitals, Md.	1935-1944	82	1.2

doubt, drain" or "when in doubt, don't drain." It was evident, too, that some of the residents and younger surgeons were not quite sufficiently knowledgeable in exercising correct judgment in the more difficult cases. Measures to improve such situations will be presented later under "Suggestions for reducing the mortality." Table III illustrates mortality figures in some of the other hospitals in this particular type of appendicitis.

There were three deaths in this group during the last five-year period. The ages were 3, 48 and 57, and the latter two were obese. Only one presented a typical history, another had chills and fever with no localization of pain, and the child complained of sore throat, cough and emesis, followed only later by abdominal cramps. The McBurney incision was used in all. The appendix was gangrenous in each instance and was grossly perforated in two. These two were drained. All received local sulfonamides and two were given parenteral administration in addition. The immediate postoperative course was stormy in all, with marked distention, requiring Miller-Abbott decompression. Type III pneumonia was the cause of death on the 5th day in the case of the child. The second patient also died on the 5th day from pyelphlebitis and bacteremia, and the third case succumbed on the 10th day from massive embolism. Autopsies were obtained on the two adults. The chief contributory factors in causing death were obesity, difficulty in diagnosis, distention, a silent

phlebothrombosis, and existing upper respiratory infection in the case of the child. Distention is certainly one of the important predisposing causes of thrombosis, with its threat of infarction or embolism. Fever and chills were ominous symptoms in the patient dying from pylephlebitis and sepsis, but such symptoms do not necessarily presage a fatal outcome.

FIG. 7

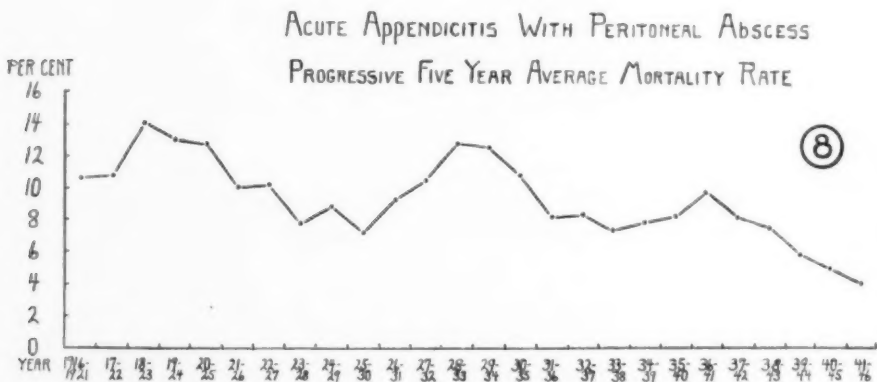
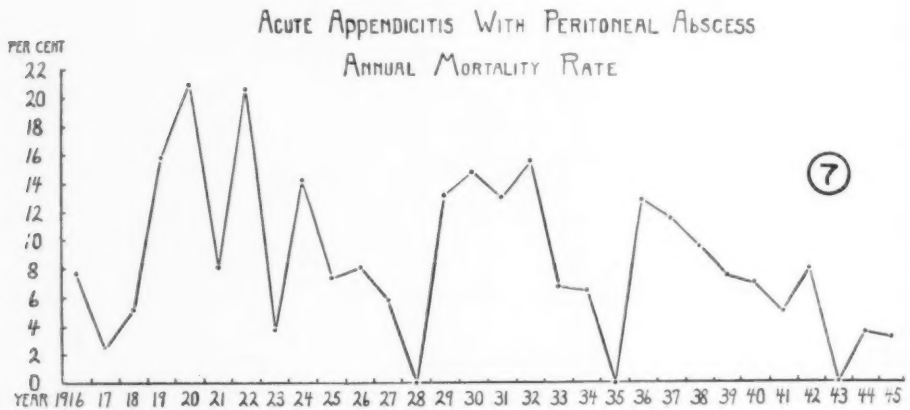


FIG. 8

FIG. 7.—Graph showing the annual death rate from 1916 to 1945, inclusive, in 896 cases of acute appendicitis with peritoneal abscess. Total number of deaths: 81; mortality rate, 9.04 per cent. Mortality rate for 1945 was 3.45 per cent.

FIG. 8.—Graph for comparison with that in Figure 7, showing the progressive five-year average death rate from 1916 to 1945, inclusive, in all cases of acute appendicitis with peritoneal abscess. Mortality rate for 1941 to 1946 was 4.16 per cent.

ACUTE APPENDICITIS WITH PERITONEAL ABSCESS

There were 896 cases of primary appendiceal abscess, this comprising 16 per cent of the whole series. The 81 deaths in this subgroup produce a mortality of 9.04 per cent. In Figure 7 one notes a high rate of 20 per cent in

ACUTE APPENDICITIS

1920 and 1922 while in 1928, 1935 and 1943 it was zero. The last year of the present study shows a mortality rate of 3.45 per cent. The progressive five-year average (Fig. 8) reveals a steady decline since the 1936-1941 period, and the last five-year interval registers a mortality of 4.16 per cent, a little less than half the total rate for this group. Our results are therefore encouraging.

In Table IV comparable rates from other hospitals are shown, but does not include any series treated conservatively or by delayed methods of therapy.

There were four deaths from appendiceal abscess in the last five-year period. Three patients were elderly (60, 71 and 78) and obese. The fourth patient was 36. Severe hypertension was observed in the 60-year-old patient. The duration of illness was two days, five days (in two), and two weeks. Only one presented a typical history, but it was suggestive in another. Two took

TABLE IV

MORTALITY RATES FROM ACUTE APPENDICITIS WITH APPENDICEAL ABSCESS, REPORTED IN LITERATURE					
Year of Publication	Author	Place	Period Studied	No. of Cases	Mortality per cent
1940	Boyce ⁷	Charity Hospital, La.	1930-1939	323	10.8
1940	Reid and Montanus ⁴²	Cincinnati General Hospital, Ohio	1934-1938	129	10.0
1940	Stafford and Sprong ³²	Johns Hopkins Hospital, Md.	1931-1939	283	7.06
1941	Nassau, Lorry and Pulaski ³⁷	Frankford Hospital, Pa.	1904-1939	135	8.8
1941	Rumbold ⁴⁴	Genesee Hospital, N. Y.	1925-1939	130	18.4
1942	Cutler and Hoerr ¹⁵	Peter Bent Brigham Hospital, Mass.,	1913-1940	247	7.3
1942	Slattery and Hinton ⁴⁹	Bellevue Hospital (IV Div.), N. Y. C.	1928-1939	88	7.9
1942	Stafford ⁴¹	Johns Hopkins Hospital, Md.	1939-1941	42	2.38
1943	Budd and Watkins ⁹	Cleveland Survey, Ohio	1940-1941	113	9.7
1945	Aycock and Farris ³	Baltimore City Hospitals, Md.	1935-1944	58	6.9

cathartics. One patient was observed for a week after admission and another underwent decompression with a Miller-Abbott tube for several days before operation. The McBurney incision was employed in three, but a left rectus was chosen in the fourth because this was the most prominent region of the abscess. Twice the surgeon encountered serious technical difficulties. The appendix was not removed in two others. Spinal anesthesia was administered twice and nitrous oxide-ether was chosen for the other two. Sulfonamides were introduced locally in two, but all received parenteral sulfa therapy. Penicillin was used, in addition, for one patient. The immediate postoperative reaction was quite satisfactory in three, but one developed moderate distention on the following day. One patient (with hypertension) died on the second day from massive pulmonary embolism and acute pulmonary edema. Another succumbed on the 5th day from paralytic ileus and type VI pneumonia. There was also a question of a flare-up of a quiescent pulmonary tuberculosis. Neither of these cases were autopsied. The third patient (with incision and drainage of appendiceal abscess only) had a smooth postoperative course and was allowed up on the 11th day. Six days later he went into sudden collapse and died. Autopsy revealed a large saddle embolus at the bifurcation of the

pulmonary artery. There was a bilateral phlebothrombosis of the external iliac and femoral veins. The peritoneum was clean except for the region of the appendiceal abscess. The appendix was laterocecal with a perforation 5 cm. from the base. There was no clinical evidence of thrombosis during the postoperative period. The fourth patient (watched for one week after admission; incision and drainage of appendiceal abscess only) suffered a long difficult postoperative course. A secondary intraperitoneal abscess was incised and drained ten days after operation. Six days later he revealed a pneumonitis in the right lower lobe. On the 26th day, there was evidence of a pylephlebitis, followed by incision and drainage of a left subphrenic abscess on the 40th postoperative day. This required revision in another ten days. Blood culture

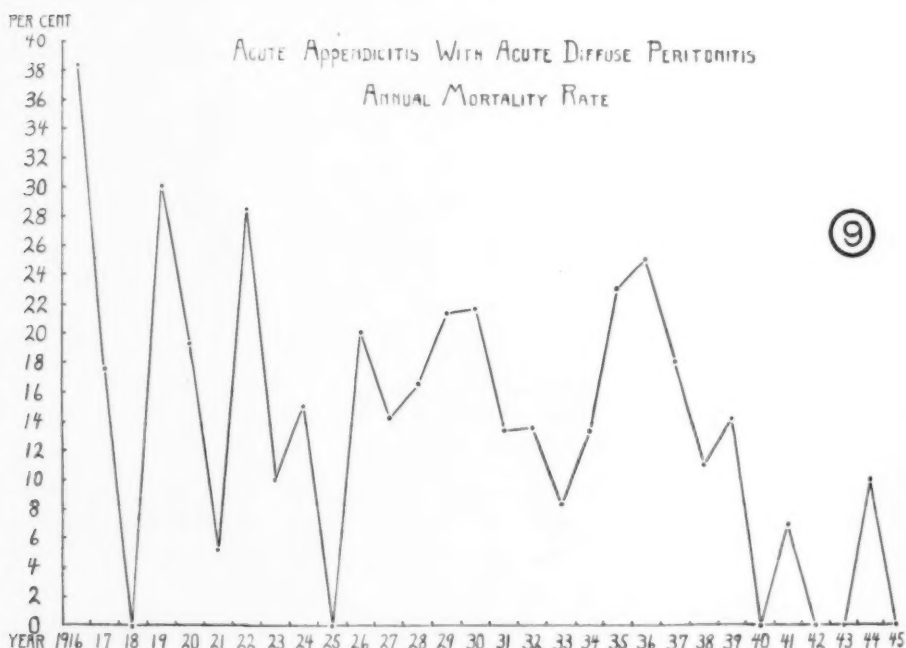


FIG. 9.—Graph showing the annual death rate from 1916 to 1945, inclusive, in 452 cases of acute appendicitis with acute diffuse peritonitis. Total number of deaths: 70; mortality rate: 15.48 per cent. No deaths in 1945.

on the 45th day disclosed a non-hemolytic streptococcus. A left suppurative pleurisy then developed which required drainage on the 52nd day. He continued to worsen, his general sepsis could not be controlled, and he expired on the 90th postoperative day from bacteremia, pylephlebitis, meningitis or metastatic cerebral abscesses. No autopsy was obtained.

The chief factors in these four deaths were advanced age in three, obesity in two, hypertension in one, unrecognized diagnosis in two, and failure to appreciate a postoperative bilateral femoral phlebothrombosis.

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ACUTE APPENDICITIS WITH ACUTE DIFFUSE PERITONITIS

Four hundred fifty-two cases, 8.34 per cent of the total number, revealed a diffuse, or spreading peritonitis, at the time of operation. There were 70 deaths, producing a mortality rate of 15.48 per cent. Figure 9 illustrates the annual mortality rate and during the first 20 years the rate was quite high, although there were two years (1918 and 1925) without any deaths. In the past nine years there has been a marked diminution in the

TABLE V

MORTALITY RATES FROM ACUTE APPENDICITIS WITH ACUTE DIFFUSE PERITONITIS, REPORTED IN LITERATURE

Year of Publication	Author	Place	Period Studied	No. of Cases	Mortality per cent
1941	Nassau, Lorry and Pulaski ¹⁷	Frankford Hospital, Pa.	1904-1939	356	23.6
1941	Rumbold ⁴⁴	Genesee Hospital, N. Y.	1925-1939	145	18.0
1942	Slattery and Hinton ¹¹	Bellevue Hospital (IV Div.), N. Y. C.	1928-1939	48	33.3
1945	Aycock and Farris ¹	Baltimore City Hospitals, Md.	1935-1944	116	25.0

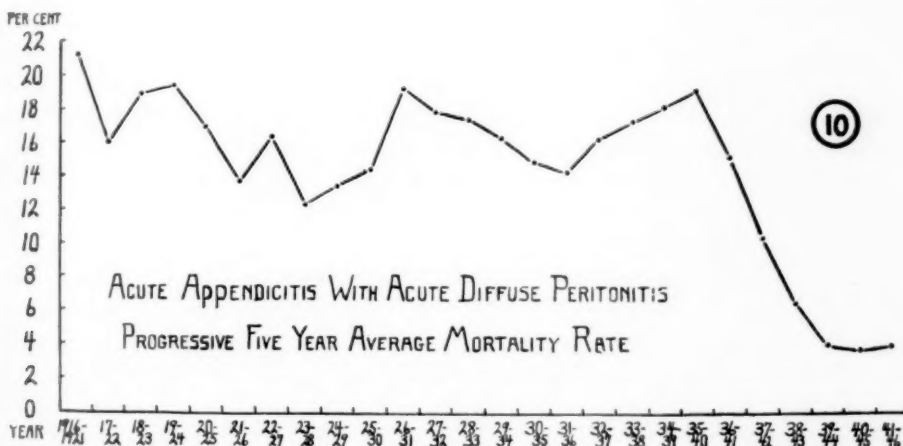


FIG. 10.—Graph for comparison with that in Figure 9, showing the progressive five-year average death rate, from 1916 to 1945, inclusive, in all cases of acute appendicitis with acute diffuse peritonitis. Mortality rate for 1941 to 1946 was 4.08 per cent.

death rate, and no fatalities took place in 1940, 1942, 1943 and 1945. The progressive five-year average (Fig. 10) illustrates this rather strikingly, particularly from the 1936-1941 period to the latest one (1941-1946) which registered a mortality rate of 4.08 per cent.

Table V illustrates comparable figures in other hospitals but excludes results obtained from conservative or delayed operative treatment.

Two deaths are recorded in the past five years. One was 54 and the other was 82 years old. Both were thin. The former had a one day atypical, and the latter a two day typical history. There was marked hypertension and cardiac enlargement in the elder one. The diagnosis in the younger patient

was perforated peptic ulcer, so that an upper right rectus incision was made. It was necessary to extend it caudad. The appendix was lateroretro cecal, with a perforation near the base. There was no evidence of a localizing process. He took the anesthesia very poorly and it was necessary to resort to open ether. Culture of the pus revealed five organisms, indicating the severity of the infection. A McBurney incision with local anesthesia was chosen for the elder patient. A meso-cecal gangrenous appendix was found with a perforation at the middle third. Thin odorless pus was welling in from all sides of the operative field. The culture grew out a non-hemolytic *b. coli*. Five grams of sulfanilamide were placed into the operative field. Removal was technically difficult. The immediate postoperative reaction was rather severe in both patients. They received parenteral sulfa therapy, and penicillin was administered to the younger patient, in addition. He also required decompression with the Miller-Abbott tube. Bilateral pneumonia developed over both bases at the end of 24 hours and he died of shock and overwhelming infection 50 hours after operation. No autopsy was obtained. The elder patient responded rather well during the first postoperative week. She then incurred bilateral pneumonia in the second week. During the following week there was evidence of cul-de-sac abscess, and this ruptured spontaneously per vagina. For some unexplained reason, a rectovaginal fistula developed in the fourth week and on the 28th postoperative day there was a sudden severe hemorrhage from the abscess and fistula site, and she died soon after. Autopsy showed a clean peritoneum, a small residual abscess in the left lower quadrant, and the cul-de-sac abscess communicating with the rectovaginal fistula. No specific bleeding point was found.

The important factors which played a role in these two deaths were age, atypical history, wrong preoperative diagnosis, hypertension, misplaced incision, poorly tolerated anesthetic, technical difficulty at operation, pneumonia, overwhelming polybacterial infection, and a severe fatal hemorrhage.

ACUTE APPENDICITIS WITH ACUTE PROGRESSIVE FIBRINOPURULENT PERITONITIS

Fortunately there were only 34 such cases in the present series, or 0.6 per cent. All but six died. The death rate is therefore very high, namely 82.35 per cent. There was only one survival amongst the five cases during the last five-year period.

The four deaths are briefly presented. They were in the middle age group, ranging from 37 to 53. The sexes were equally divided. The duration of illness ranged from two to ten days. Three were obese. All presented atypical histories. One patient (age 53) was diagnosed as renal colic. Twenty-four hours later the diagnosis was changed to acute cholecystitis. Six hours later he was taken to the operating room with a diagnosis of gangrenous cholecystitis with perforation. Two incisions were made: a paracostal over the gall-bladder and then a McBurney incision with drainage of an appendiceal abscess. He died in the operating room just as the dressings were applied. Autopsy revealed a fibrinopurulent peritonitis; a retrolatero cecal abscess,

with a gangrenous perforated appendix fixed to the posterior cecal wall. Culture of the peritoneal pus grew out a *b. coli*.

The second patient (age 51) was admitted in shock, with a diagnosis of perforated peptic ulcer, having acknowledged a 24-year ulcer history. In spite of supportive treatment, he never recovered from shock and died soon after admission. Autopsy showed a generalized fibrinopurulent peritonitis, a perforated gangrenous appendix lying in the pelvis and a healed duodenal ulcer.

The third patient (age 42) was thought to have an acute ileus secondary to adhesions from radiotherapy, or to recurrence of an ovarian carcinoma. Because the maximum signs presented in the left lower quadrant, a left lower rectus incision was made under local anesthesia. A fibrinopurulent peritonitis was encountered and, because of the patient's precarious condition, no further exploration was made. She died six hours after operation. Autopsy disclosed a generalized fibrinopurulent peritonitis, a large abscess behind the terminal ileum and cecum extending to the sigmoid on the left and to a pelvic mass below. A perforated necrotic appendix extended into the abscess.

The last patient (age 37) was admitted with a diagnosis of acute cholecystitis and only after 24 hours' observation was the true nature of the disease process suspected. Through a McBurney incision, a high retrocecal and retrocolic gangrenous perforated appendix was found. The surgeon experienced considerable technical difficulty in the procedure and it was hard to control bleeding. There was a generalized fibrinopurulent peritonitis in addition. In spite of local and parenteral sulfonamide therapy, transfusions, and decompression with the Miller-Abbott tube, she had a very stormy course and died on the third postoperative day. A blood culture was sterile. Peritoneal culture grew out a *b. aerogenes*. At autopsy there was a widespread fibrinopurulent peritonitis. A culture of the heart's blood revealed an anaerobic green streptococcus.

The chief factors in the mortality amongst these four cases are: Wrong diagnosis, resulting in serious delay in two instances, obesity in three, two incisions in one case, serious technical difficulties with bleeding in another, and general sepsis, collapse, and shock in all of them.

Figure 11 reveals the progressive five-year average curves for all cases of acute appendicitis (curve V), together with the various subgroups, excepting acute appendicitis with generalized fibrinopurulent peritonitis. These curves therefore reflect their relationship, one to another, and reveal the general mortality trends over the period of time under study. As already noted, there has been a definite rise in mortality from acute appendicitis with acute local peritonitis and our chief concern, therefore, is directed to this subgroup.

Table VI illustrates the mortality rate for all cases of acute appendicitis; as well as each of its subgroups, for the 30-year span; also the most recent five-year period, and the last year of the study. It is gratifying to note that the mortality rates in the middle column are very much better than those in the first column, whilst those in the right hand column are even lower than

those shown in the middle one. Attention is also directed to column one where the mortality rate quadruples with spread of the disease in the earlier phases. It nearly doubles in rate between abscess and diffuse peritonitis, and then increases almost sixfold between acute diffuse peritonitis and fibrinopurulent peritonitis.

GENERAL REMARKS

The diminution in our appendicitis fatalities is in keeping with similar reports from other hospitals and clinics. In fact, a marked reduction has taken place throughout the nation since 1930. In that year the mortality was 15.3 per 100,000 whilst in 1945 the rate was 5.1 per 100,000,⁵⁸ or 6,697 deaths.

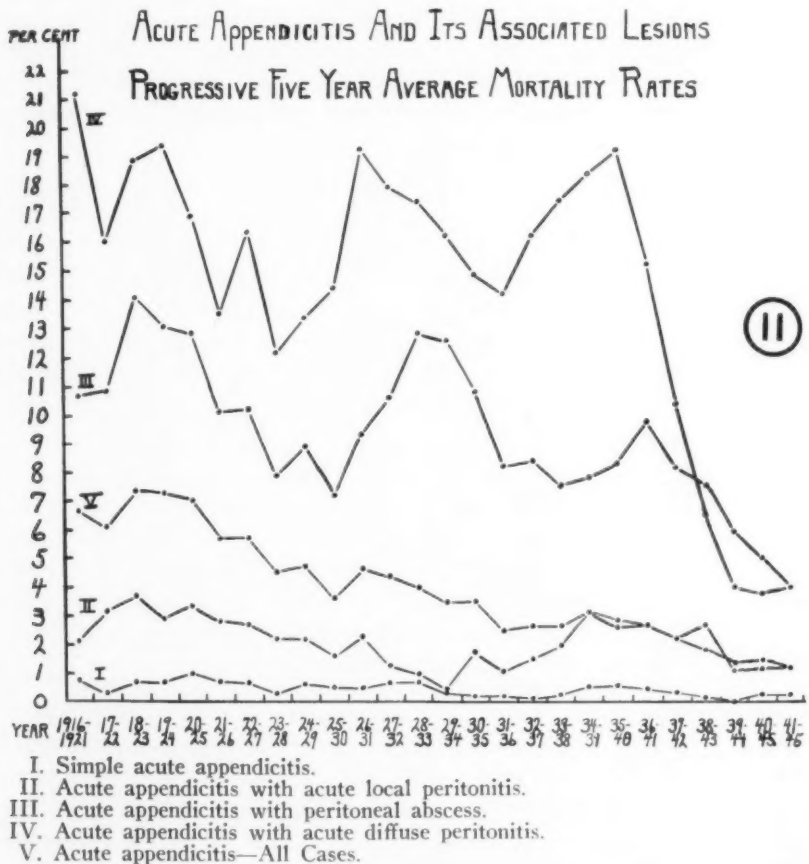


FIG. 11.—Graph showing the progressive five-year average mortality curve from 1916 to 1945, inclusive, for all cases of acute appendicitis and its associated lesions (curve V) as well as its various subgroups (curves I to IV) with the exception of subgroup comprising acute appendicitis with progressive generalized fibrinopurulent peritonitis.

With so little value placed on human life in recent years, this death rate is small indeed, yet it seems that we really should exert our every effort to reduce it further.

ACUTE APPENDICITIS

There are numerous reasons for this nationwide reduction in appendicitis deaths. The coordinated plans on the part of the public health service combined with the sponsorship of local medical societies, industries, insurance companies, schools, universities, and municipal authorities have served to render the laity conscious of two serious dangers of appendicitis, namely, delay and purgation. In our own series we find that there is a slight but definite reduction of our peritonitis cases, even though our annual incidence of acute appendicitis remains about the same. This suggests that the population in our area has become appendicitis conscious, or that the physicians, serving this region, are recognizing and diagnosing the disease process early and promptly.

Another factor in reducing appendicitis mortality has been the more thorough teaching and training of our residents. During our most recent five-year period, there were more deaths incurred by the attending than by the resident staff.

TABLE VI

ACUTE APPENDICITIS AT THE PRESBYTERIAN HOSPITAL, NEW YORK CITY
January 1, 1916 to December 31, 1945

Classification	Mortality Rate 1916-1945	Last Five Year Average Mortality Rate	1945 Mortality Rate
All cases of acute appendicitis.....	3.55%	1.37%	0.43%
Simple acute appendicitis.....	0.49%	0.39%	0.00%
Acute appendicitis with acute local peritonitis....	2.06%	1.35%	0.00%
Acute appendicitis with peritoneal (appendiceal) abscess.....	9.04%	4.16%	3.45%
Acute appendicitis with acute diffuse peritonitis..	15.48%	4.08%	0.00%
Acute appendicitis with progressive fibrinopurulent peritonitis.....	82.35%	80.00%	*0.00%

* No cases for 1945.

The past decade has witnessed great advances in the care and treatment of the sicker type of patient, for instance, preoperative preparation, appreciation of fluid balance requirements, deficiency states such as anemia and hypoproteinemia, more liberal use of plasma, blood, and oxygen therapy, gastrointestinal decompression, means of anticipating and controlling thrombophlebitis with its threat of infarction or embolism, and early ambulation. Of great importance has been the marked advance in methods of anesthesia and in its skillful administration. The advantage of utilizing the services of a highly trained staff of well trained and resourceful anesthetists is obvious. In close association with the latter, there has been a steady improvement in operative technic, with fewer technical errors and blunders, together with the more frequent use of the McBurney incision.

A further factor in the diminution of appendicitis fatalities has been the advent of the antibacterial agents. The role of the sulfonamides is known to all, and everyone is familiar with the reports of Ravdin, Lockwood and Rhoads,⁴⁰ Harvey, Meleney, and Rennie,²¹ Mueller and Thompson,³⁴ Jackson and Coller,²³ Thompson, Brabson and Walker,⁵⁵ Stafford,⁵¹ Chesterman,¹¹ Aycock and Farris³ and numerous other observers. We have not employed it

consistently or set down any rigid rules with reference to its use, but prefer to leave the decision with the surgeon, who will base his judgment on the merits of any given case. The writer is disposed to use it locally and systemically in patients with local or widespread peritonitis, and to employ it parenterally in cases of appendiceal abscess. The more recent reports of Altemeier,¹ Crile,^{12, 13} Crile and Fulton,¹⁴ Fauley and his associates,¹⁶ and others, suggest that large doses of penicillin probably inhibit the escherichia organisms and may be beneficial in polybacterial peritonitis of appendiceal origin. The results of the last two groups of investigators may necessitate a change in our present policy of treating appendiceal abscess and spreading appendiceal peritonitis. Perhaps, in the discussion, Doctor Lockwood will relate his interpretation of the mechanism and mode of action of penicillin on the gram negative intestinal bacilli in connection with appendiceal peritonitis. We have used penicillin, both alone and in conjunction with the sulfonamides, but we have not a sufficient number of cases on which to base any conclusions. The use of streptomycin in appendicitis with peritonitis or abscess is still speculative, but a preliminary report on experimental peritonitis in dogs by Zintel and his associates⁶⁰ suggests that it is not as helpful as the combined effect of penicillin and the sulfonamides.

We are also impressed by the causes of death during the last five-year period of our study, in that our improved methods of therapy appear to have diminished the fatalities from peritonitis, general sepsis, pneumonia and embolism. The chief factors in our recent deaths are: Advanced age, hypertensive cardio-vascular disease, obesity, diabetes, atypical history, wrong diagnosis, and technical errors such as misplaced incisions, difficulty in removing the appendix, and lack of understanding the indications for drainage. Other factors were improper choice of anesthetic, failure to recognize a latent thrombophlebitis and inability to control distention.

One must not neglect to pay tribute to the greatly depleted attending staff, and the resident and assistant resident surgeons, with their accelerated and shortened training period, who, during the war years, continued to maintain a low mortality record at this hospital. (Fig. 1).

Thus there are many factors responsible for the lowered mortality rate of acute appendicitis but perhaps the most important of all are the sober judgment, skill, and experience of the surgeon combined with his observance of fundamental precepts and sound surgical principles.

SOME PRACTICAL CONSIDERATIONS

Our general policy has been one of prompt operation, and we fully concur with the arguments, for early surgical intervention, as set forth by Stone,⁵³ Ogilvie,³⁹ Stafford and Sprong,⁵² Gile and Bowler,¹⁸ Maes and his associates,³⁰ Shipley,^{47, 48} Thornton,⁵⁶ Nichols,³⁸ Mueller,³³ Lahey,²⁷ Scott and Ware,⁴⁶ and numerous others. When necessary, our patients may undergo several hours of preparation before operation, including resuscitative measures and restoration of fluid balance. This form of therapy is not to be construed as "delayed"

treatment in the sense employed by the more conservative school of surgeons.

The type of anesthetic should be chosen by the anesthetist, after due appraisal of the case with the surgeon in charge. This tends to minimize the danger of routine and rule of thumb methods. The writer is disposed to favor spinal anesthesia, whenever it is considered safe, because of complete wound relaxation and relatively greater ease in exposing the site of pathology without undue retractor trauma. However, there are numerous occasions when a patient's condition does not permit the use of spinal anesthesia and, in such instances, we resort to some other anesthetic agent. As Rogers and Faxon⁴³ have indicated, the operation should not exceed an hour. There are rare exceptions to this. Speed is desirable at times but never at the expense of technical precision and gentleness to the tissues.

The McBurney incision is extensively employed at this institution, but if circumstances indicate the advisability of another approach, we do not hesitate to do so. Doctor Whipple has repeatedly stated: "Fit the incision to the patient, not the patient to the incision." A liberal incision is desirable and, if technical difficulties are encountered in satisfactorily demonstrating our surgical objective, the incision should be enlarged—caudad by Weir extension, or, if necessary, division of the outer portion of rectus muscle and sheath;—cephalad by transecting the internal oblique and transversus abdominis muscles.

The intelligent use of retractors is often overlooked, resulting in unnecessary roughness and trauma to the wound. Since most of these wounds are contaminated by reason of the infected appendix, the danger of intramural infection becomes increasingly greater by overzealous retraction on the part of the second assistant. Retractors should be inserted and placed with great care and exactness, and the operator should frequently admonish his assistant to exert minimal force consistent with adequate exposure.

The appendix should be sought with extremely careful manipulation and maneuvers, and with the least possible disturbance of the surrounding viscera. It may be necessary, at times, to divide the lateral peritoneal reflection of the cecum in order to mobilize a high retrocolic appendix. Division of a thick, friable, edematous mesoappendix must be executed with the greatest care and gentleness because, if this structure tears, the blood vessels retract, and oftentimes it is almost impossible to control the resultant bleeding. We prefer to invert the appendix stump but simple ligation is quite proper, particularly when the adjacent cecal wall is thickened and friable. We strongly condemn combined ligation and inversion of any appendix stump.

If it is decided to drain (*vide infra*) a case of local peritonitis, it is better to insert one or two simple Penrose or cigarette drains. These should be removed relatively early, depending, of course, on the general condition of the patient, the temperature curve, the amount and character of the discharge, the bacteriology of the pus, and the region and anatomical peculiarities of the area drained. For primary appendiceal abscess, it is preferable to introduce a tampon, with gauze packs or cigarette drains placed within it. This permits

free drainage, keeps the wound well "sprung," thus preventing narrowing or "bottle necking" of the superficial portion of the tract, and, lastly, encourages healing from within out, by arresting premature infolding of the adjacent intraperitoneal structures. Sometimes we introduce a small soft rubber tube or catheter along the lateral aspect of the tampon for purpose of subsequent irrigations. In any event, it is extremely important *never* to insert a drain *across* a viscus if it can possibly be avoided. This is one of many reasons for choosing the McBurney incision because it lends itself so well in the proper placement of drains.

If, in the removal of an unperforated gangrenous appendix, the surgeon decides against intraperitoneal drainage, it is wise to insert a small drain to the muscle or properitoneal layer, because such wounds are almost certainly heavily contaminated. No possible harm can come from this, and the surgeon enlists an added factor of safety for his patient. Elderly, obese and diabetic individuals should also receive intramural drainage even though the peritoneum may be closed.

The reader is familiar with present-day methods of postoperative therapy, but there is one point which deserves special emphasis, namely, the desirability of medical teamwork. This is particularly important in connection with older patients. Too often we are inclined to "wait and see," only to call upon our medical consultants when signs of heart failure or pneumonia or apoplexy have already set in. It is far preferable to invite medical council before anything serious has taken place. Such close association between surgeon and internist may forestall many serious complications.

INDICATIONS FOR DRAINAGE

For many surgeons, the problem of drainage seems to progress in cycles. In the beginning, one usually starts with a firm resolve to follow the principles governing drainage. In due course of time, a tendency develops to overlook the teachings of medical school and early intern days. As experience increases, the surgeon may discard or revise the precepts of his instructors. This in itself is not reprehensible because progress demands vision and imagination, as well as reflection and deliberation. But sooner or later, a time arrives when boldness and self-confidence will outbalance sound judgment and critique. Then comes the final step—a serious oversight or blunder, resulting in a severe and stormy postoperative course, perhaps in death. At Staff Conference, the case is reported and discussed, the error is recognized and acknowledged. There is the usual expression of remorse and regret, followed by a reaffirmation of the indications for drainage. This marks the beginning of the next cycle, and others to follow. Unfortunately, with the advent of antibacterial agents and better methods of treatment, it is tempting and misleading to overlook sound fundamental principles of surgical therapy.

For teaching purposes, and particularly for interns and residents, and also for younger members of attending surgical staffs, the indications for drainage are herewith presented. They should be observed by surgeons of average

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ability, such as Doctor Jones, Doctor Smith, Doctor Brown and myself. To the highly skilled, experienced master surgeon, some of these suggestions will appear superfluous and perhaps even unnecessary:

- Presence of an abscess.
- Necrotic or compromised tissue remaining in the operative field.
- Inability or inadvisability to remove the focus of infection (appendix)
- Gross contamination from:
 - perforation of appendix
 - break in technic
- Extensive exposure of retroperitoneal tissue.
- Uncontrolled bleeding.
- Insecure ligation or closure of the appendiceal stump.
- Severe operative trauma.

There are certain corollaries to these rules, such as an extremely difficult technical procedure with retrograde removal of the appendix; also the presence of two or more organisms in the direct smear of the exudate or pus. In addition, there are also some variable factors which may enter into a decision to drain, namely, age, debility, cachexia, obesity, diabetes, and other constitutional diseases. The indications for drainage of the intramural portion of these wounds have already been discussed. If the thoughtful conscientious surgeon will keep these criteria for drainage clearly in mind, he will have no need for untimely and ill conceived catch phrases to misguide or influence his final decision. He can act without fear or misgiving. Application of these principles governing drainage will contribute, in no small measure, to a substantial reduction of deaths, especially in the subgroup of acute appendicitis with local peritonitis. Severe postoperative reactions and serious complications will also diminish in this particular subgroup.

SUGGESTIONS FOR FURTHER REDUCTION OF MORTALITY FROM ACUTE APPENDICITIS

The continuation of public education in the dangers of purgation and delay, and in the advantages of early diagnosis and prompt operation, in acute appendicitis, should be vigorously supported by appropriate local, state and national authorities and agencies. The results of such concerted action are already known, and they have contributed greatly toward the reduction of appendicitis deaths in the nation as a whole.

In our institution, we believe a further diminution in mortality can be effected as follows:

- Earlier recognition of atypical cases.
- Require the attending surgeon, on call, 1) to examine all cases of uncertain or equivocal diagnosis,
 - 2) to scrub with the resident or assistant resident if the patient
 - a) is obese
 - b) is 45 years or over
 - c) gives a 48-hour history, or longer
 - d) presents a doubtful diagnosis.

Careful planning with reference to operative preparation and approach, proper choice of anesthesia, and postoperative care.
Anticipation and prevention of complications, particularly thrombophlebitis, severe distention, and spread of intra-abdominal infection.
Unceasing efforts to improve operative technic.
Recognition of indications for drainage.
Close teamwork with the medical staff in any case presenting potentially serious non-surgical complications.
Continued study of experimental peritonitis, particularly along lines described by Kay and Lockwood.^{25, 26}
Early ambulation in selected cases.
Annual review, at surgical staff conference, of acute appendicitis, together with a discussion of complications, methods of treatment, death analysis, and suggestions in formulating our policy for the ensuing year.

SUMMARY

A study of the mortality from acute appendicitis, at a University Hospital, covering a period of 30 years, has been presented.

There has been a satisfactory progressive over-all reduction in the mortality rate, which is in keeping with reports from other hospitals and in the nation as a whole.

The reasons for such a general diminution in appendicitis deaths have been noted.

The various subgroups in our series have also shown a substantial decline except for Acute Appendicitis with Acute Local Peritonitis, which disclosed an increased mortality rate. Some of the factors responsible for this rise have been discussed. Suggestions have been submitted to improve and control it.

Appendicitis deaths, during the last five-year period, have been somewhat different from those analyzed in the earlier years of this study. There are proportionately fewer fatalities from intraperitoneal infections and complications, and relatively more from cardiovascular and other nonsurgical conditions.

We have reviewed the indications for drainage and have emphasized a few practical points in operative technic and management of acute appendicitis.

A plan for further improvement of our appendicitis mortality rate has been submitted.

In the light of recent reports and investigations, it may become necessary and advisable to change the present policy of treatment for appendiceal abscess and diffuse peritonitis at this institution.

REFERENCES

- ¹ Altemeier, W. A.: *Surg. Gynec. & Obst.*, **81**, 375, 1945.
- ² Aud, G.: *South. M. J.*, **34**, 914, 1941.
- ³ Aycock, T. B. and E. M. Farris: *ANNALS OF SURGERY*, **121**, 710, 1945.
- ⁴ Barrow, W. and A. Ochsner: *J. A. M. A.*, **115**, 1246, 1940.
- ⁵ Bohmanson G. and E. B. Norrup: *Act. Chir. Scandinav.*, **84**, 427, 1940-1941.
- ⁶ Bower, J. O.: *Pennsylvania M. J.*, **43**, 1145, 1940.
- ⁷ Boyce, F. F.: *New Orleans M. & S. J.*, **93**, 300, 1940.

ACUTE APPENDICITIS

- 8 Boyce, F. F. and H. E. Nelson: *South Med. & Surg.*, **103**, 588, 1941.
- 9 Budd, J. H. and R. M. Watkins: *Ohio St. M. J.*, **39**, 433, 1943.
- 10 Burke, J. and H. F. Kuhn: *Surg. Gynec. & Obst.*, **72**, 578, 1941.
- 11 Chesterman, J. T.: *Lancet*, **2**, 407, 1944.
- 12 Crile, G., Jr.: *Am. J. Surg.*, **72**, 859, 1946.
- 13 Crile, G., Jr.: *Surg. Gynec. & Obst.*, **83**, 150, 1946.
- 14 Crile, G. Jr., and J. R. Fulton: *U. S. Nav. Bull.*, **45**, 465, 1945.
- 15 Cutler, E. C. and S. O. Hoerr: *J. Michigan M. Soc.*, **41**, 203, 1942.
- 16 Fauley, G. B., T. L. Duggan and R. T. Stormont: *J. A. M. A.*, **126**, 1132, 1944.
- 17 Faxon, H. H. and H. Rogers: *N. E. Journ. Med.*, **226**, 746, 1942.
- 18 Gile, J. T., and J. P. Bowler: *J. A. M. A.*, **103**, 1750, 1934.
- 19 Haggard, W. D., and J. A. Kirtley, Jr.: *J. Tennessee M. A.*, **34**, 97, 1941.
- 20 Hall, R. J.: *New York Med. Jour.*, **43**, 662, 1886.
- 21 Harvey, H. D., F. L. Meleney, and J. W. R. Rennie: *Surgery*, **11**, 244, 1942.
- 22 Hathaway, H. R., and R. M. Watkins: *Ohio State M. J.*, **39**, 247, 1943.
- 23 Jackson, H. C., and F. A. Collier: *J. A. M. A.*, **118**, 194, 1942.
- 24 Jennings, J. E., H. H. Burger, and M. Jacobi: *Arch. Surg.*, **44**, 896, 1942.
- 25 Kay, J. H., and J. S. Lockwood: *Surgery*, **20**, 56, 1946.
- 26 Kay, J. H., and J. S. Lockwood: *Surgery*, **21**, 155, 1947.
- 27 Lahey, F.: *S. Clin. North America*, **22**, 783, 1942.
- 28 Lockwood, J. S.: *J. A. M. A.*, **115**, 1190, 1940.
- 29 Lockwood, J. S., and I. S. Ravdin: *Surgery*, **8**, 43, 1940.
- 30 Maes, U., F. F. Boyce, and E. M. McFetridge: *New Orleans M. & S. J.*, **87**, 24, 1934.
- 31 Meyer, K. A., W. H. Requarth, and D. D. Kozoll: *Am. J. Surg.*, **72**, 830, 1946.
- 32 Morse, L. J., and M. J. Rader: *ANNALS OF SURGERY*, **111**, 213, 1940.
- 33 Mueller, R. S.: *ANNALS OF SURGERY*, **122**, 625, 1945.
- 34 Mueller, R. S., and J. E. Thompson: *J. A. M. A.*, **118**, 194, 1942.
- 35 Muller, G. P.: *J. M. Soc. New Jersey*, **37**, 587, 1940.
- 36 Murphy, J. J., R. G. Ravdin, and H. A. Zintel: *Surgery*, **20**, 445, 1946.
- 37 Nassau, C. F., R. W. Lorry, and E. J. Pulaski: *Arch. Surg.*, **42**, 296, 1941.
- 38 Nichols, H. M.: *West. J. Surg.*, **49**, 480, 1941.
- 39 Ogilvie, W. H.: *Guy's Hosp. Gaz.*, **47**, 225, 1933.
- 40 Ravdin, I. S., J. S. Lockwood, and J. E. Rhoads: *Pennsylvania M. J.*, **43**, 1100, 1940.
- 41 Ray, B. S.: *New York State J. Med.*, **38**, 412, 1938.
- 42 Reid, M. R., and W. P. Montanus: *J. A. M. A.*, **114**, 1307, 1940.
- 43 Rogers, H., and H. H. Faxon: *New England J. Med.*, **226**, 707, 1942.
- 44 Rumbold, L.: *Arch. Surg.*, **42**, 25, 1941.
- 45 Schullinger, R. N.: *Arch. Surg.*, **32**, 65, 1936.
- 46 Scott, W. H., Jr., and P. F. Ware: *Arch. Surg.*, **50**, 258, 1945.
- 47 Shipley, A. M.: *New England J. Med.*, **219**, 333, 1938.
- 48 Shipley, A. M.: *South Surg.*, **3**, 308, 1934.
- 49 Slattery, L. R., and J. W. Hinton: *Am. J. Surg.*, **57**, 294, 1942.
- 50 Smith, M. K.: *S. Clin. North America*, **19**, 277, 1939.
- 51 Stafford, E. S.: *Surg. Gynec. & Obst.*, **74**, 368, 1942.
- 52 Stafford, E. S., and D. H. Sprong: *J. A. M. A.*, **115**, 1242, 1940.
- 53 Stone, H. B.: *Va. Med. Jour.*, **103**, 1750, 1934.
- 54 Tashiro, S., and M. M. Zininger: *Arch. Surg.*, **53**, 545, 1946.
- 55 Thompson, J. E., J. A. Brabson, and J. M. Walker: *Surg. Gynec. & Obst.*, **72**, 722, 1941.
- 56 Thornton, G. L.: *Lancet*, **1**, 1256, 1938.
- 57 Turner, G. G.: *Brit. M. J.*, **2**, 4056, 1938.
- 58 U. S. Public Health Service: *FSA-216*, **27**, Dec. 1946.
- 59 Young, J. R.: *South. Med. & Surg.*, **102**, 470, 1940.
- 60 Zintel, H. A., M. Wiley, A. Nichols, and J. E. Rhoads: *Surgery*, **21**, 175, 1947.

DISCUSSION.—DR. FREDERICK A. BOTHE, Philadelphia: The Appendicitis Mortality Committee of the Philadelphia County Medical Society analyzed the deaths from appendicitis in 17 hospitals in Philadelphia during 1944. Our analyses for the years 1945 and 1946 are not completed at this time. Eight of the 17 hospitals were teaching institutions and many of the surgeons in the other nine were connected with a teaching institution. The Philadelphia Department of Public Health cooperated in this study by sending a copy of the death certificates of all patients dying from appendicitis to the Secretary of the Philadelphia County Medical Society. A comprehensive questionnaire was filled out for all deaths.

In the 17 institutions noted above there were 4997 cases of appendicitis operated upon in 1944; 3248 for acute appendicitis without perforation, 1328 for acute appendicitis with perforation and its sequela, and in 421 patients chronic appendicitis was found. We are only a fact-finding committee; however, an analysis of the deaths as they occurred in these 17 hospitals revealed several interesting facts:

In the 4997 cases there were 47 deaths. The time that elapsed between the onset of symptoms and the patient having consulted a physician was less than six hours in 13 instances, six to 24 hours in 15 instances, one or more days in 26 instances and two or more days in 19. We then studied the time that elapsed after the physician was called before the patient was hospitalized. In 28 cases it was less than six hours, in 32 it was less than 24 hours, in 15 it was more than 24 hours and in 12 it is more than three days. We tried to ascertain whether or not a cathartic had been taken before hospitalization. In 22 cases no cathartic was taken, eight patients had given themselves a cathartic and the physician had ordered one in two instances. In 15 cases we were unable to determine whether or not a cathartic was given. The findings at operation showed acute appendicitis in five cases, perforation with generalized peritonitis in 17, perforation with abscess formation in 15, chronic appendicitis in one, normal appendix in one, findings indefinite in three and no operation was performed in five cases.

We noted in four instances that there was a marked delay in obtaining surgical consultation after the patient was admitted to the hospital. These cases had been admitted to the medical service instead of having the benefit of immediate medical and surgical consultation. In one case the surgeon was not called for 12 hours, in two cases not for 24 hours and in one, more than 36 hours. This prompted us to request that all patients hospitalized with abdominal pain should have both surgical and medical consultation immediately upon admission. In an effort to determine whether the person performing the operation contributed to these deaths we studied who had performed the operation. It was found that the attending surgeon operated upon 30 of these patients, the associate on five and the resident on 12.

There were nine deaths in known cardiacs, occurring eight to ten days after the operation. This was rather surprising as we had felt that cardiac cases under the care of a cardiologist prior to surgery would be more likely to succumb in the first 72 hours after operation. There were seven deaths from pulmonary embolism. This again demonstrates the high percentage of patients who died from this serious postoperative complication, and emphasizes the value of a femoral or higher ligation as an aid in preventing its occurrence.

DR. ROY D. MCCLURE, Detroit: Dr. Arthur McGraw, who is unavoidably absent today, was stimulated by Dr. Schullinger's abstract to look up our statistics. At Henry Ford Hospital during the ten years from 1937 to 1946, there were 13 deaths following 1405 appendectomies for acute appendicitis, an over-all mortality of 0.92 per cent. In the same year drainage only was performed in 68 cases of appendix abscess with one death, a mortality of 1.5 per cent. During the last five years there has been but one death in 601 appendectomies for acute appendicitis; during the last four years, no deaths in 466 similar appendectomies.

This reduction in mortality cannot be attributable to penicillin because that drug

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became available for unrestricted use only in 1946. Though used to some extent, sulfonamides have probably not been a large factor in improved mortality. The Wangenstein principle of gastroduodenal decompression and drainage has been available to us and used through the ten-year period, the Miller-Abbott tube for only a few less years. Both methods, however, have undoubtedly been of greatest help in the most recent years by reason of their more frequent, skillful and therefore effective use. Increasing and more intelligent attention to maintenance of electrolyte, metabolite and water balance has undoubtedly been a large factor. It is interesting to note, however, that the only probably helpful factor virtually restricted to the last five years is early ambulation.

In addition, several points in technic which we have adhered to for the past 25 years may have a favorable influence on appendectomy mortality: (1) Favoring the muscle-splitting incision; (2) identifying the appendix by locating its origin at the convergence of the three longitudinal striae of the cecum rather than by searching for the tip with the index finger; (3) avoidance of "packing off" of the peritoneal cavity; (4) avoidance of drain material any heavier or stiffer than rubber dam.

BRIEF SUMMARY—HENRY FORD HOSPITAL: 13 post-appendectomy deaths.

Duration of symptoms—one-half day to 12 days

Causes of death:

Diffuse peritonitis	4	
Multiple abscesses	2	
Paralytic ileus	1	
Pulmonary embolus	4	
Lung abscess and pneumonia	1	
Addison's Disease	1	13

Clinical findings:

Simple acute appendicitis	1	
Acute with perforation or gangrene	9	
With localized abscess	2	
With localized peritonitis	2	
With diffuse peritonitis	5	

Autopsies 6, or 47 per cent.

HENRY FORD HOSPITAL: APPENDECTOMY FOR ACUTE APPENDICITIS DURING LAST TEN YEARS

Deaths	Years	Cases	Mortality
13	10	1405	0.92%
7	9	1234	0.57%
6	8	1060	0.56%
3	7	891	0.34%
3	6	709	0.42%
1	5	601	0.17%
0	4	466	0.00%
0	3	325	0.00%
0	2	190	0.00%
0	1	108	0.00%

DR. JOHN S. LOCKWOOD, New York: It is a pleasure to have the opportunity of discussing Dr. Schullinger's paper and to remark first on the fact that Dr. Schullinger has acted as a very efficient one-man committee in Presbyterian Hospital for a number of years in carefully following our experience with acute appendicitis and keeping close tab on the results. In spite of the splendid record many hospitals can now present, I do not think we ought to become in any way smug about the results, because patients with peritonitis still show a significant mortality rate. In analysis of the explanation for the progress in the last few years, I think the outstanding accomplishment has been through recognition of the fact that peritonitis is a local disease which produces a very profound systemic reaction and that in effect, it causes death through shock, and the methods of treatment of peritonitis which have been conspicuously effective have been those which increase the patient's tolerance to the shock-promoting factors in the disease; more delib-

erate, careful pre-operative preparation; correction of metabolic, electrolyte and water balance; use of blood, plasma and oxygen; gastro-intestinal decompression and, finally, administration of chemotherapeutic and antibiotic agents. Obviously, it becomes exceedingly difficult to evaluate in any mathematical way the relative significance of any one factor in treatment, and certainly that is true so far as chemotherapeutic agents and antibiotics are concerned.

Through the opportunity I have had during the last three years to study the physiologic aspects of experimental appendicitis in the dog, I have become convinced that an important role of chemotherapeutic and antibiotic agents is their ability to modify the severity of the toxic reaction of the host to bacteria and bacterial products in the peritoneum. One effect of the sulfonamides, penicillin and streptomycin is to interrupt bacterial synergism, which is of outstanding significance in this type of peritonitis. Even though the drugs may not be active against all the flora involved, their ability to restrain growth activity of gram positive cocci seems to modify the tendency of the disease to spread. Second, there is the ability of the sulfonamides and penicillin to limit the production of bacterial toxins and thereby to minimize the "dose" of toxic protein split-products which the patient must absorb. One mechanism we have been interested in is the apparent ability of the sulfonamides and penicillin directly to neutralize the action of the toxic bacterial proteins which are elaborated by the types of organisms involved in peritonitis. And, finally, of considerable importance is the ability of these agents to encourage production of a fibrin barrier around the focus of infection.

DR. GROVER C. PENBERTHY, Detroit: At the meeting of this Association in 1942, Drs. Benson, Weller and I reported a study of 1653 cases of appendicitis covering a 15-year period (1927-1941) at the Children's Hospital of Michigan. The mortality in the acute ruptured diffuse peritonitis was 64.9 per cent, with many of this group moribund on admission. The over-all mortality, including all types, was 4.2 per cent.

In the period 1939-1941 a study of the group with peritonitis or abscess was made, as to the effect of chemotherapy on the mortality rate, and in the 47 cases treated with chemotherapy the mortality was 2.1 per cent; in the 67 cases not treated with the sulfa drugs the mortality was 11.9 per cent.

In contrast with the above, from 1942 through 1946, 435 infants and children have been operated upon for appendicitis; of this group 104 had perforated appendices with peritonitis. These patients have had the benefit of surgery and chemotherapy, which represents both sulfa and penicillin therapy, in addition to adequate amounts of blood combined with fluids sufficient to maintain a proper mineral and electrolyte balance with control of distention by intubation and suction drainage. In this entire group of 435 patients there has been no mortality. Fewer of the patients with peritonitis have had peritoneal drainage and it is our belief that it has reduced the incidence of post-operative intestinal obstruction.

Our study confirms the results reported by Dr. Schullinger, and we congratulate him and his associates on their results.

DR. JOHN A. MCCREERY, New York: It might be of interest to compare Dr. Schullinger's results with those of a suburban hospital of 150 beds in which most of the surgery is done by seven or eight men who probably have not the same average ability or experience as the visiting staff at the Presbyterian. This may be balanced by the fact that the community is intelligent and health conscious, as evidenced by the fact that more than 70 per cent of our cases have been operated on within 24 hours of the onset of symptoms.

In 1941 Dr. Serrell and I published in *Surgery** our results in 525 cases of acute appendicitis operated on in the Greenwich Hospital during the period from June 1, 1933, to December 31, 1939. In this series there were seven deaths, one in a patient with local peritonitis, the other six with diffuse peritonitis. All these cases died of continuing peri-

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toneal sepsis. During the period from January 1, 1940, to December 31, 1946, there were 515 cases with six deaths. In only one of these was death the result of continuing peritoneal sepsis. The only change in our procedure in this time is more meticulous care in maintaining fluid balance and the more general use of the sulfa drugs, both local and general, 186 of the 515 having been treated with sulfa. Of the six deaths, one was in a patient who was admitted with an abscess; one died suddenly of massive pulmonary embolism while up and about and ready for discharge; one patient had been a hemiplegic for five years and died of cardiac failure. The remaining three cases were in the older age group, one 77 and another 70. These three complained of acute abdominal pain from eight to ten days after operation and rapidly developed signs of peritoneal irritation and obstruction. At operation all three had necrosis of the terminal ileum thought to be due to mesenteric thrombosis. All three had evidence of marked cardiovascular disease.

We all hope for a mortality of zero in acute appendicitis, but we must realize that with increasing longevity and the increasing number of patients above 60 years of age, appendicitis may be cured and yet the patient dies of some underlying condition while still in the hospital. These cases must be recorded as deaths from appendicitis, which is inaccurate unless statistics are broken down more completely.

DR. RUDOLPH N. SCHULLINGER, New York (closing): The speaker desires to thank Dr. Bothe, Dr. McClure, Dr. Lockwood, Dr. Penberthy, and Dr. McCreery for their interesting and informative comments. Dr. McClure's record is one toward which all of us are attempting to strive. Dr. Lockwood dilated on the protective mechanism in peritonitis, which of course arouses the attention of us all. Dr. Penberthy's report on the mortality in children is interesting, particularly in view of Dr. Taylor's study at the Babies' Hospital in Columbia Medical Center. In the period from 1935 to 1939 he found two deaths, and from 1940 to 1944, two deaths. So he was not certain what role some of the newer methods of treatment might play in reducing the mortality amongst children. Dr. Bothe's comments shed additional light on some of the responsible factors in appendicitis mortality between the time of onset of the acute attack and the time of operation. Delay and catharsis are not always the patient's fault. Dr. McCreery's figures are illustrative of the good work accomplished by smaller staffs in smaller institutions, and one sincerely hopes this is true for all other similar hospitals throughout the country.

STUDIES UPON SPINAL CORD INJURIES*

I. The Development of Automatic Micturition

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MANY OF THE COMPLICATIONS which arise from injury to the spinal cord, other than the paraplegic state, have an important bearing upon the prognosis of the patient. The function of the urinary bladder; the occurrence of root, visceral, and diffuse burning pains; the development of mass reflexes and spasms; dysfunction of the autonomic nervous system; the treatment of decubitus ulcers; urinary tract calculi, and the many psychological and emotional problems which beset the patient are some of the factors which seriously affect his rehabilitation. The care of the patient with a spinal cord injury is not solely one of attempting to make him walk. He presents a serious general medical problem and requires the combined efforts of those well-trained in every field of medicine and surgery. Fortunately, some of these patients improve so that these efforts need not be specifically concentrated but the majority require continued, careful supervision to insure their maximum rehabilitation.

Our studies are based on an experience with 471 patients with injuries of the spinal cord. Of these, 416 were patients injured in military service and 55 were civilian patients. Of the military patients, 115 were examined and studied in an overseas theater of war as early as one hour to two or three weeks after injury and as late as 122 days after injury. Satisfactory follow-up data has been maintained upon 18 of these patients. The other 301 patients were observed in a Veterans Administration Hospital and their histories in some instances cover a period of five years following injury. The civilian patients have been observed in certain instances for as long as 20 years. Among the patients of a military status, 295 received open wounds of the spinal cord from bullets or shell fragments, while 121 suffered closed injuries, exemplified by the common fracture-dislocation of the spine. Among the civilian patients, only eight were injured by open wounds, and 47 sustained closed injuries of the spinal cord. In the two groups of patients with the closed type of injury, traffic, diving, and wrestling accidents were most common.

The establishment of efficient urinary function is one of the primary goals in the care of the patient with an injury of the spinal cord. It avails little to rehabilitate the patient successfully in various other spheres if eventually he does not have adequate control of his urine, for in such a chronically disabled patient the inability to void with some means of control will alone prevent his return to a socially acceptable state. Furthermore, proper urinary function, in so far as it can be developed, is important for the preservation of life itself.

* Read before the American Surgical Association, March 25, 1947, Hot Springs, Va.

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THE IMPORTANCE OF EARLY CARE

Urinary function in our patients has appeared in one of the following five forms: (1) early return to normal micturition, (2) eventual return of partial voluntary control of micturition, (3) involuntary dribbling of urine, or the frequent uncontrolled passage of very small amounts of urine, (4) absolute retention, a less common situation, and (5) automatic or reflex micturition, entirely free of any voluntary effort of the patient. If complete, normal urinary control, or partial voluntary control aided by special efforts on the part of the patient to empty his bladder, can not be obtained, the ideal condition is that of automatic micturition. Proper care of the bladder in the early stages of treatment is most important to insure the development of reflex emptying of the bladder when any return of normal power is impossible. Under ideal conditions an indwelling urethral catheter placed immediately after injury, properly serviced, and connected with a tidal drainage apparatus adjusted for the particular needs of the patient, will lead to automatic micturition within a few weeks. The shortest period for such reflex function to become established in our patients was at the end of five weeks, in a patient with a lesion at the fourth thoracic cord segment. Such function was established in one patient with a complete lesion of the conus medullaris and cauda equina at the end of two and one-half months. In both instances the patient had no other type of bladder drainage than that of a small caliber Foley catheter. Tidal drainage was used from the beginning, urinary sepsis was kept at a minimum, urinary calculi did not develop, and the nutritional state of the patients remained good. In numerous instances we have found proof of the efficacy of the indwelling catheter with tidal drainage not only in the establishment of automatic micturition but also as an aid in restoring partial voluntary control. In no case did automatic micturition develop while a suprapubic catheter was in place. On the contrary, many patients developed such urinary control following the removal of the suprapubic tube, placement of an indwelling catheter and training for a period of time thereafter with tidal, or carefully controlled manual drainage. Severe urinary infection soon after injury was found to prolong greatly or obviate completely the development of automatic micturition, and such an infection many times has been observed to destroy an already well established automaticity.

Among the patients of military status, various methods of urinary drainage had been used in the early days and weeks of treatment. These included (1) allowing the bladder to distend and overflow, (2) manual expression, (3) perineal urethrostomy, (4) suprapubic cystostomy, (5) repeated urethral catheterization, and (6) an indwelling urethral catheter. The exigencies of war alter treatment, but it is a moot question as to whether suprapubic drainage is necessary for purposes of transportation. Ample evidence is at hand that many suprapubic tubes, ostensibly placed for such purposes, were initially placed too high or too low and thereafter neglected so that they became the source not only of severe urinary sepsis but also of the additional complication of bedsores. Petroff¹ and other recent writers have pointed out the fact that

the elimination of the suprapubic tube, repugnant to most patients, is an important factor in the improvement of the patient's morale. When a comparison is made between the advantages of early indwelling catheter drainage and prolonged suprapubic drainage, it is immediately obvious that automatic micturition is encouraged by the use of the indwelling catheter and made impossible by the suprapubic tube.

THE LEVEL OF THE LESION

Automatic micturition may occur in the presence of a complete lesion at any level in the cord or cauda equina. In 77 patients with cervical lesions, 11, or 14.3 per cent, eventually developed automatic micturition. In 288 patients with lesions at various levels of the thoracic cord, 97, or 34 per cent, eventually developed such reflex activity. In the 106 patients with lumbo-sacral lesions, 17, or 16.4 per cent, developed automaticity. Under favorable conditions, therefore, automatic micturition may develop and continue regardless of the level of the lesion. It is not uncommon for the automaticity to be interrupted and require a secondary period of training when such complications as urinary sepsis, calculi formation, nutritional debility, decubiti, or severe mass reflexes occur. Automatic micturition develops most rapidly when the lesion lies below the 7th cervical cord segment and above the 5th thoracic. There is an increase of the time required for its development as the incidence of the lesions descend into the lower thoracic cord, and most patients with lesions of the conus medullaris or of the cauda equina require from 8 to 20 months, or longer, to develop automaticity. Therefore, our experiences corroborate the fact pointed out many years ago by Head and Riddoch² that the completely isolated bladder without any intact distal segment of spinal cord can under the proper conditions develop and maintain the state of automatic reflex emptying.

Severe retention, as well as frequent dribbling of urine, with large residual capacities up to 1,200 cc. in either condition, has been observed in the presence of a complete or partial lesion, at any level of the cord or cauda. We have found numerous instances of dribbling with high grade retention in many of our patients with cervical or thoracic cord lesions whose early care was punctuated with many complications, or who were early denied the benefits of an indwelling urethral catheter and tidal drainage training. The occurrence of severe mass spasms of the extremities is of common occurrence with lesions of the cord, and severe spasms usually so affect the bladder that it takes part in the general somatic spasm and tends to evacuate small amounts of urine at frequent intervals. Under such conditions it may contract down to a very small capacity, usually with little or no residual. These mass spasms affecting the bladder and lower extremities are of decreasing incidence as the lesions descend the cord and cauda below the 10th thoracic segment.

In the presence of lower thoracic or caudal lesions, where there is still some power of contraction in the abdominal muscles, the patient is aware of the need to void by such signs as a feeling of abdominal distention, burning or

tenseness in the genitalia, suprapubic cramping sensations, or tenseness, burning, and drawing sensations in the lower extremities. When the lesion lies above the 9th or 10th thoracic segments, distention of the bladder and a warning of impending micturition may be manifested by such signs as flushing of the face, arms and chest; perspiring on the upper half of the body; a feeling of sudden heat over the face and neck; nausea, or sudden severe headache. In the rare patient these latter signs may also be present with lower thoracic or caudal lesions, but in any event the symptoms are promptly relieved upon the emptying of the bladder. Upon becoming aware of such signs, many patients can initiate urination by such extravescical stimuli as massaging the lower abdominal wall, rubbing the skin of the inguinal region, tugging on one spermatic cord, or pinching the skin of the thigh. Patients with lesions of the conus or cauda do not respond as readily to such extravescical stimuli as do those with higher lying lesions. Yet if they are unobstructed at the bladder neck they may eventually develop some particular stimulus which will aid starting of the urinary stream, and while their automaticity is less likely to be efficient, they can aid the emptying of the bladder by suprapubic pressure and by holding the breath and tensing the abdominal muscles.

In those patients who void every 2 to 15 minutes in small amounts and who usually hold a large residue of urine, the least straining such as coughing, sneezing, laughing, or hearing a sudden loud noise may cause them suddenly to wet themselves. Such patients are therefore forced to keep in place a urinal, to wear a clamped off urethral catheter, to use a penis clamp, or to wear a rubber urinal, none of which is an ideal situation for the control of the urine. Many of these patients are found to have greatly hypertrophied bladder necks, and the operation of transurethral resection of the ring of hypertrophied muscle has been successful in transforming such patients into a state of automatic micturition, with almost complete emptying every one to three hours. They are frequently relieved, also, of the uncomfortable burning in the groin, flushing of the face, perspiration and headache which accompany such frequent spasmodic attempts of a bladder working against resistance. Not only is the patient freed of a restraining and embarrassing condition, but the bladder, without a high residual urine, shows a much cleaner urine following such an operation.

The amount of residual urine in the automatic bladder varied widely among our 471 patients. Of these patients 26.3 per cent, or 125, eventually developed automaticity, or had it over a period of time during some phase of their observation. Residuals have been found varying from a few cubic centimeters to as high as 500 cc. It can not be said that a bladder which acts reflexly every two or three hours but which leaves behind a high residual content is a successfully functioning bladder, and residuals as low as 50 cc. or less may lead to sepsis or calculus formation. It has been common to find patients who were discharged to their homes for a period of time, with good automatic bladder function, return to the hospital weeks or months later with nutritional difficulties, decubiti, or urinary sepsis, with complete or nearly

complete loss of their automatic micturition. We have been impressed by the ease with which automatic activity of the isolated bladder is altered or lost. Such reflex activity needs constant aid and supervision, but even once lost it can be re-established by patient care through the use of an indwelling catheter, tidal drainage or carefully managed manual irrigation, and the elimination of such complications as have been named.

THE EXTENT OF THE LESION

It is not always possible to determine accurately the degree of residual neurologic function in the incomplete lesion of either the cord or the cauda equina, and likewise the degree of voluntary control over urination can not always be determined. Any patient who can actually feel the passage of urine within the urethra obviously is not voiding by automatic micturition, though it is true that in such patients the act may be started by an extravesical stimulus such as massage of the groin. Partial voluntary control and the effectiveness of extravesical stimuli may exist simultaneously. Urinary sepsis, calculus formation, and a large amount of residual urine may exist in these patients as they do in those with complete neurologic lesions.

One patient was seen who sustained a stab wound of the spinal cord at the midthoracic level, with a resulting most accurate Brown-Sequard syndrome. At no time did he ever have any loss of voluntary control over urination. Four other patients who sustained shell fragment wounds of the lower cervical and upper thoracic cords with a production of modified Brown-Sequard syndromes were seen early after injury, and they likewise did not suffer any urinary difficulties.

SUMMARY

Automatic micturition will develop following a complete lesion at any level within the spinal cord or cauda equina. It appears earlier and with greater efficiency in the presence of lesions between the levels C. 7 and Th. 5. It does not appear in the presence of incomplete lesions of the cord, though the effect of extravesical stimuli on the initiation of urination may be quite similar in the case of either a complete or partial lesion. Extravesical stimuli are in any event less effective in the presence of lesions below the 10th thoracic segment. Automatic micturition may occur with remarkable regularity at intervals as long as three hours, but with very low efficiency as determined by a large residual amount of urine. Lesions of the conus and cauda do not produce the striking viscerovisceral reflexes, such as flushing, perspiring, headache, or reverse peristalsis such as may appear in the presence of high lesions in the cord, and the appearance of such reflex phenomena in severe form, with or without massive spasm of the lower extremities, may spell the termination of efficient automatic micturition.

Cystometric examination at regular intervals will indicate when the catheter may be removed to allow the trial of automatic micturition, indicating that a reflex response to bladder wall tension is necessary for this activity.

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Automatic micturition will develop only when there is no mechanical bladder neck obstruction and when the sphincter is capable of reflex relaxation. Extravesical stimuli are an aid but not a necessity to the development and maintenance of automatic micturition. Automaticity will not develop in the patient with severe bladder sepsis, multiple calculi, or a condition of severe debilitation.

BIBLIOGRAPHY

- ¹ Petroff, B. P.: The Paralyzed Patient: Urologic Aspects. *J. A. M. A.*, **129**, 154, 1945.
- ² Head, H., and G. Riddoch: The Automatic Bladder, Excessive Sweating and Some Other Reflex Conditions, in *Gross Injuries of the Spinal Cord*. *Brain*, **40**, 188, 1917.

THE CONTROL OF CANCER*

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INTRODUCTION

THE DEATH TOLL FROM CANCER has been steadily rising, chiefly due to the older average age of the population, and last year there were 181,000 dead. Since cancer is not a reportable disease, there are no accurate figures on incidence, but surveys¹ indicate there are approximately 310,000 new cancer cases each year. It is estimated that there are 700,000² persons in this country who are under treatment for cancer at any one time. There is evidence of increasing public interest in the control of cancer as shown by a recent Gallup survey, which indicated that 72 per cent of the people were willing to pay more taxes in order to have better control of cancer.

The control of cancer requires research, education, and service to the cancer patient. All this involves the medical profession, the hospitals, the public health service, nursing service, schools, universities, and other groups. Obviously, no one agency, governmental or private, has sufficient resources to cope with a problem of this magnitude. The necessity for seeking the assistance of all groups is apparent. The keynote of effective cancer control must be the cooperation and coordination of all groups dedicated to this task. Since the voluntary health agency exists for the purpose of assisting the people to meet a health menace not controlled by other organizations, its most important function may be as a coordinating agency.

The American Cancer Society may best serve the people and the medical profession by remaining a dynamic force, so flexible that it may render assistance wherever the need is greatest, rather than to become static by assuming a permanent maintenance responsibility. Its most valued service may be to show the need, point the way to better cancer control, and demonstrate the method by which this may be achieved. The ultimate goal of the voluntary health agency is to bring disease under control, and so to eliminate itself by removing the reason for its existence.

OVERALL PLANNING

The need for a more intensive effort to control cancer is apparent. The scope of the various activities involved in the control of cancer is so great that no one group, the medical profession, the U. S. Public Health Service, the American Cancer Society, or the private foundations can accomplish the goal unaided. For this reason there is a need for a cooperative, coordinated effort within the framework of an overall plan of attack. This is necessary if the most effective use is to be made of our limited resources, men, and material.

Funds available for the support of cancer research in the past have been

* Read before the American Surgical Association, March 25, 1947, Hot Springs, Va.

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inadequate, but even if adequate financial support were available, overall planning is needed in the interest of economy and efficiency. During the year 1946 the funds available for cancer research were as follows:

American Cancer Society	\$2,500,000
U. S. Public Health Service	1,772,000
All private foundation funds	650,000
Total	<u>\$4,922,000</u>

Thus our national expenditure for cancer research was at the low rate of \$27.19 per death caused by cancer. At the same time we live in an economy where more than this amount was spent to advertise one brand of cigarettes and four times this amount was spent for hair tonic. Plainly, as a nation we have not given due consideration to the facts and the resources needed for an overall attack to control a major health menace.

There is also a shortage of trained personnel and facilities for both research and the care of the cancer patient. Since time will be required to build laboratories and hospitals and even more time to train personnel, the need for a coordinated overall plan rather than competition between interested groups is apparent.

The control of cancer may be accomplished by two major lines of attack:

1. The maximum use of the present methods of prevention, diagnosis, and treatment.
2. Research for new methods.

The only methods at present available for the treatment of cancer are surgery, x-ray, and radium. The importance of surgery in the treatment of cancer, the importance of cancer to the surgeon, and the public interest in this problem warrant a discussion of the role of surgery.

In order to make the maximum use of surgery in the prevention, diagnosis, and treatment of cancer there are four objectives to be achieved:

1. Early recognition of the signs and symptoms of cancer is necessary so as to cause the potential patient to seek the advice of a physician early in the course of the disease. While this is a problem of lay health education, the content of knowledge is medical. Further, while this problem more properly lies within the field of activity of the lay educator, the general practitioner, and the internist, the surgeon because of his wider experience in the treatment of cancer has a responsibility in promoting such education. Unfortunately, all cancers do not give early signs and symptoms, or they exist in a part of the body where they cannot be seen or felt by the patient. For some time, regular semiannual physical examinations have been advocated to meet this problem. Cancer detection centers or prevention clinics have been set up in New York, Philadelphia, Chicago, and other cities. These clinics have reported finding approximately 1.5 per cent of cancer in supposedly well persons. This is more cancer than has been estimated to exist in our population. Statistics as to the incidence of cancer, however, are so inadequate that these figures may be more nearly correct than the previous estimates. Macfarlane³ found 10 can-

cers in 10,325 examinations in 550 female volunteers, an incidence of 2 per cent or 0.1 per cent of the examinations. In addition, numerous other abnormalities requiring medical attention were detected. *There is no doubt that regular physical examinations will detect many unsuspected cancers in an early curable stage of the disease.* It appears that the value of the semiannual physical examination should be measured in terms of the general health problem and its educational value, rather than in terms of cancer alone. If a semiannual physical examination is to become part of our national health program, a re-evaluation of the number of physicians required for the nation is indicated. Approximately 95 per cent of all cancers are found in the 59,000,000² people who are over 35 years of age. Assuming one-half hour per examination, a biannual physical checkup would require 59,000,000 physician hours, or the full time of approximately 30,000 physicians. It should not be assumed that this is an impossible task because of the number of physicians required, nor that cancer detection or health maintenance centers could be put into operation immediately for the entire nation. Rather it emphasizes the need for planning; because if such a national program is to be realized within a ten-year period, we must plan now to train the necessary personnel and provide the required facilities. In the meantime, the need for cancer detection* in supposedly well persons is established, and every effort should be made to extend its application. There is need for data to determine the type of history and physical and laboratory examination which may yield the maximum result with the greatest economy.

There is an urgent need for medical schools and hospitals to establish pilot cancer detection or health maintenance centers to study these problems and to establish techniques for screening large groups of the population. Such pilot clinics may also provide an invaluable service as postgraduate teaching centers. Medicine as a social science must face this problem, the scope and importance of which demands an experimental approach to insure acquisition of basic information.

Surgery cannot yield a high degree of success unless cancer is treated before the disease has spread to distant parts. It is, therefore, apparent that the public must know what potential cancer symptoms are so that it may seek aid early in the course of the disease. It is also well established that many cancers do not give early symptoms but can be detected on physical examination. While the relative value of lay health education and the regular physical examination has not been determined, it is apparent that both are necessary steps in effective cancer control. Finally, for those cancers which do not give early symptoms and which cannot be detected on physical examination, research is needed to establish more effective screening technics.

2. The second important objective is early diagnosis, which is primarily a responsibility of the medical profession. The physician is directly liable for

* The term detection is here used to indicate the detection of cancer in supposedly well people who have no complaints. It is suggested that the word prevention should be limited to the eradication of supposedly precancerous lesions.

the delay in 25 per cent of cases and shares the responsibility with the patient in another 15 per cent.^{4, 5, 6} While the patient is culpable for most of the delay in superficial cancer, the physician assumes the major responsibility as the cancer becomes more inaccessible, requiring special laboratory, x-ray, or endoscopic examination. This points the need for better professional education in the diagnosis of cancer, since wrong advice is frequently given. It also suggests that lack of availability of proper diagnostic facilities may be an important factor. There is too frequently a tendency to treat cancer of the internal organs as a benign or functional lesion until proven to be otherwise. This does not imply a knife diagnosis, but earlier and more adequate study if the cause of the complaint is unknown.

It behooves those of us who are teachers of medicine and surgery to inquire as to why this situation should exist. Are our textbooks so written as to make clear that cancer of the internal organs, such as the lungs and gastro-intestinal tract, cannot be diagnosed by the history and physical examination? Do we spend too much time demonstrating advanced cancer and too little emphasis on the steps necessary to diagnose early cancer? Is the training of specialists on a sufficiently broad basis to make clear the danger of inadequate general physical examinations? Does the instruction in physical examination make clear its limitations as well as its potentialities?

As lay health education becomes more effective, causing an alert public to seek earlier diagnosis, the diagnostic problem for the physician will become more difficult. Has the time come to re-evaluate some of the criteria we have used in teaching the diagnosis of cancer in the past? In an already overcrowded curriculum, is adequate time and skill devoted to the second most common cause of death?

It is clear that the average physician is increasingly in need of help in the diagnosis of early cancer. More studies are needed to indicate what type of assistance, in what age groups, and where it is most needed. Are facilities for diagnosis available to the average physician adequate to meet the need? Have we devoted sufficient attention to postgraduate education for the doctor who is not privileged to work in a hospital or medical school? The American Cancer Society, believing that there is a need for postgraduate cancer education, proposes to publish a concise professional journal dedicated to this purpose. Until such time as research makes available better and simpler methods of diagnosis, we have no choice but to make the maximum use of the methods we now have.

3. The third requirement is prompt treatment. Early detection and diagnosis may be of little value unless treatment is rendered promptly. Procrastination by either the doctor or the patient may be fatal. The "shopping" habit of patients going from one doctor to another seeking a favorable opinion and general lack of health education contributes to delay. Also in recent years the shortage of hospital beds, with delays in admission because of long waiting lists, is a contributing factor.

4. The fourth objective is adequate treatment. Until research reveals new

and better methods of treatment, the chief hope of the cancer patient lies in surgery. The developments in surgery have been great and show promise of keeping pace with the increased demands of cancer patients if treated in time. There is, however, a lag between the potentialities of treatment as demonstrated in the best clinics and the average result found in the average hospital available to the average patient. This is of especial significance, because the average physician is more likely to be influenced by the results he has experienced in his own patients rather than those reported in some far away clinic. There is a great need to study the results of treatment in larger and unselected groups of the population, and to find ways and means of making better treatment available to more people.

The Tumor Committee of the Connecticut State Medical Society in collaboration with the State Department of Health in 1934 developed a system for the study of cancer in 27 general hospitals. This offered the first opportunity to determine the effectiveness of present methods in treating cancer in a large section of the population. The first study was done on 1,610 cancers of the rectum admitted to hospitals between 1935-45.⁷ During 1935-40 the radical operability was 32 per cent, and during the second five-year period it rose to 44 per cent. For the same period the largest clinic in New England reported an operability of 83.5 per cent.⁸ During the first five-year period, the operative mortality in the 27 general hospitals was 25 per cent, and during the second five-year period it dropped to 18 per cent. At the same time, the operative mortality for the largest clinic in New England was under 5 per cent. The five-year cure rate for the 735 patients in Connecticut was 7.9 per cent in contrast to approximately 50 per cent for those patients entering the larger clinics.

These comparisons are not made to show that one clinic is better or worse than another, or selective, but to call attention to the fact that the average effectiveness of our present methods of treating cancer in a large group of the population is vastly different from those ordinarily reported in medical literature. The larger clinics have pointed the way and demonstrated what may be accomplished. It is the responsibility of those interested in cancer as a health menace to obtain the facts and point the way to better treatment.

The statement has been made that 30-50 per cent of those now dying of cancer could be saved by the maximum use of the present methods. It is estimated that there are 14,000 new cancers of the rectum in this country each year. If we assume the present five-year cure rate is 10 per cent, there would be 1,400 cured patients each year, leaving 12,600 who die within five years. To save 50 per cent, would require a curability approximately 5 per cent under the cure rate reported by one of the larger clinics today. It would, therefore, appear that an attempt to save 50 per cent of those now dying from cancer of the rectum is not an unreasonable goal.

CANCER RESEARCH

The second major line of attack on the cancer problem is research for

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new and better methods of prevention, diagnosis, and treatment. While there is no longer a question of the need for cancer research, there are, however, differences of opinion as to how funds may be most wisely expended, and what methods and disciplines are most urgently needed. This appears to be a natural consequence of the rudimentary state of our knowledge of cancer and diversity of interest in the problem. There is, however, a consensus of the need for more fundamental knowledge of normal growth so as to better understand the abnormal growth of cancer.

The present high development of surgery well exemplifies the wisdom of the flank attack versus the frontal assault. Discoveries in supposedly unrelated fields have made modern surgery possible. From Pasteur and wine fermentation to bacteriology and asepsis, the chemistry of ether and laughing gas to anesthesia, the chemistry of aniline dyes to chemotherapy, the physiology of moulds to penicillin, these are all examples of the potential benefits of the prepared mind on a broad research front. At the same time, the rapid development under wartime pressure of penicillin and blood substitutes are effective examples of the frontal assault by planned developmental techniques.

THE SCOPE OF CANCER RESEARCH

The complexities of the problems and the varied disciplines required all suggest the need for coordinated and integrated effort. For these reasons the American Cancer Society turned to the National Research Council's Committee on Growth for advice and guidance in planning its research program. The Committee on Growth is composed of 19 members with an executive committee, the members of which are chairmen of the divisions of physics, chemistry, biology, clinical investigation, chemotherapy, and fellowships. Each division is composed of a number of panels made up of specialists in their respective field of research. The Committee on Growth, together with the panels, numbers 120 scientists representing 48 different universities and laboratories. Requests for grants-in-aid are received by the secretary of the Committee on Growth at the National Academy of Sciences in Washington, D. C., where they are channeled through the various divisions and referred to the panels best qualified to advise on the research for which funds are requested.

Thus requests for grants-in-aid receive careful study by experts in each panel, and the chairman of each division presents his recommendations to the executive committee for final consideration, so that funds may be allocated according to the overall need. It is hoped this plan will insure that the most promising research receives adequate support, that duplication of effort may be avoided, and that eventually a better coordinated and integrated attack on cancer may be developed.

It is recognized that grants-in-aid may not provide sufficient latitude for the development of cancer research. It is expected that grants may be initiated to stimulate research in responsible institutions with established reputations

and that such funds may be used within a limited but less restricted field than the grants-in-aid.

Finally, as the need arises, it may be necessary to provide funds for developmental research, using more intensive or compartmentalized methods within institutions especially equipped and staffed for this purpose.

There is a shortage of personnel trained in the disciplines needed in cancer research. In order to fulfill this need the American Cancer Society has made funds available for research fellowships up to a maximum of \$6,000 per year for senior fellowships. Beyond this, it is hoped that more permanent posts will become available in the various universities and laboratories. It appears that one of the reasons for the scarcity of qualified personnel may be that in the past cancer research has been so frequently a dead-end street academically. It is essential that opportunity be provided for adequate careers in this difficult field of investigation.

There has been much discussion as to the place of cancer research in medical schools and whether departments of oncology are justified. It is frequently observed that no one individual can be competent in the whole field of cancer. The same reasoning could be applied equally well to a professor of medicine or surgery, and in fact, this is acknowledged by the subdivision of these departments. It appears that a serious approach to the study of cancer cannot long remain an avocation, and it is likely that tradition will make a place for new ideas within the old framework.

The study of cancer began at the bedside of the patient. It moved to the mortuary and the laboratory, but finally it must return to the patient. Clinicians are the custodians of the care of patients, and hence have a grave responsibility in cancer research. Theirs is the task of promoting research in this difficult field at the bedside. The study of cancer in the clinic has yielded the only effective modes of therapy yet available, and among these is surgery. The surgeon must now assume his obligation by participating in the teamwork needed to bring together the varied disciplines required in the new and highly specialized technics of clinical investigation.

REFERENCES

- ¹ Dorn H.: Illness from Cancer in the United States. Pub. Health Report Reprint No. 2537.
- ² American Cancer Society Statistical Department.
- ³ Macfarlane, Catherine, Margaret C. Sturgis, and Faith Fetterman: Results of a Cancer Control Research. *Med. Woman's J.*, 1945.
- ⁴ Pack, G. T., and J. S. Gallo: Culpability for Delay in the Treatment of Cancer. *Am. J. Cancer*, **33**, 443-462, 1938.
- ⁵ Harms, C. R., J. A. Plaut, and A. W. Oughterson: Delay in the Treatment of Cancer. *J. A. M. A.*, **121**, 335-338, 1943.
- ⁶ Leach, J. E., and G. F. Robbins: Causes for the Delay in the Diagnosis and Treatment of Cancer. (In press.)
- ⁷ Ottenheimer, et al.: Carcinoma of the Rectum in Connecticut. (In press.)
- ⁸ Hayden, E. P.: Surgical Treatment of Carcinoma of Rectum; Statistics on 198 Cases of Resection. *New England J. Med.*, **233**, 81-84, 1945.

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DISCUSSION.—DR. E. P. LEHMAN, Charlottesville, Va.: You have heard presented in very brief form the program of the American Cancer Society. The surgeon comes closer to the cancer patient, if only because of the need for biopsy, than does any other group in medicine. For that reason the American Cancer Society, and especially its Medical and Scientific Committee, recognizes the importance of having its program presented to and understood by this most representative group of surgeons of the country. I know and Dr. Oughterson knows that there are members of this Association who have in the past expressed disagreement with the aims and policies of the American Cancer Society. There may be good reasons for such disagreement. The Society in growing in two years from a corporation spending \$800,000 a year to one spending \$10,000,000 a year has made mistakes. It needs the wholehearted support of the surgical profession. The Medical and Scientific Committee will, therefore, welcome constructive criticism from any member of this body transmitted through Dr. Oughterson. Cancer is the leading problem of the surgeon today. The American Cancer Society is in a sense your instrument in a program of cancer control in which we are all so vitally interested.

DR. A. W. OUGHTERSON, New York (closing): I can only second what Dr. Lehman has said. Ours is a common effort against a common enemy, devoted to the common purpose of trying to find a common solution. It is our earnest desire to promote the control of cancer in the best interests of the medical profession and the nation, and we welcome your assistance and advice at all times.

THE SPECIALTY OF ANESTHESIA*
and its Application
in the Harvard University-Massachusetts General Hospital Department

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I. THE SPECIALTY OF ANESTHESIA

FACTORS THAT INFLUENCE the specialties of medicine in large part shape medical practice. It is desirable, therefore, to consider the factors of current importance in the development of anesthesia. In this, emphasis will be placed on the problems of the university and the university hospital. The anesthetist can occupy a fortunate position in these and in other institutions, if he will take advantage of his opportunity. I should like to be specific; that is, to set down what this opportunity seems to be at the present time, in terms of the strength and the weakness of anesthesia as a specialty, and then to describe, as a working example, how the views presented here have been put into practice in the organization and development of our Department.

In the first place, one must admit that a stigma is attached to anesthesia. To deny this is to evade the facts. It does exist; it need not. The plain fact is, a stigma will continue to be present until anesthesia can attract its share of able men, men who are as able as those who go into other fields of medicine. Great progress has been made by those who have been leaders in anesthesia over the past 20 or 30 years. Their good work needs to be built on and carried forward. Clearly, the central problem of anesthesia as a specialty is how to attract good men. Some aspects of this will be discussed. Grim denial that the field has weaknesses has not hidden them. It is better to face them, but at the same time some of the strong points of the specialty can be considered.

SOME WEAKNESSES

Technics Alone Are Not Enough. Anesthesia is not rich in technics, nowhere nearly as rich as surgery is. This in no way minimizes the importance of the essential anesthesia technics; but to try to attract good men on this basis alone is to fail. To insist that as much time is necessary for the technical training of the anesthetist as of the surgeon is to take an indefensible position. And yet such stands are common.

Although experience over considerable time and range of material is required for expertness, anesthesia technics can be mastered by ordinary men who are ordinarily deft, with only a modest requirement of intelligence and of knowledge and of judgment. As clinical anesthesia is taught today there is an almost overwhelming preoccupation with tools and their use. Current teaching too often stimulates only a pursuit of technical skill.

* Read before the American Surgical Association, March 25, 1947, Hot Springs, Va.

Anesthesia was developed in the clinic and has been nourished chiefly by clinicians. This may be part of the trouble. In recent years medical specialties have, to a great extent, grown through laboratory advances. Anesthesia has not fared as well on its clinical nourishment as other specialties have on a richer diet. Men who are occupied entirely in the clinic have neither the time, nor in many cases the training, to furnish their specialty with the vitality it needs for growth.

The Laboratory vs. Clinical Empiricism. In anesthesia we see an example of what happens when medicine attempts to advance chiefly through the clinic, inadequately concerned with basic problems. It is inefficient; it advances by trial and error. The weakness of this is measured in terms of lives needlessly lost. But the discouraging fact is that anesthesia must continue to depend greatly upon empiricism, at least for the time being. The almost complete mystery surrounding the mechanism of the anesthesia process itself and the invulnerability of the mystery to such attacks as have been made upon it, have done much to discourage investigation in this complex field.

Perhaps more than any other factor, the development of anesthesia has been delayed by our ignorance of the anesthesia process. One can liken the position of the anesthetist when confronted by the anesthesia process to that of the internist when confronted by a disease of unknown etiology. Under such circumstances the internist must be guided by symptomatology, and in acting on this basis he may be quite successful. Similarly, the anesthetist's handling of the anesthesia process can be conducted with considerable success on a controlling basis of symptomatology. But just as the internist's treatment of disease usually becomes enormously more efficient once he understands its etiology, so will the handling of anesthesia become much more precise once we understand the mechanism of the anesthesia process.

With the advance of science, even though the mechanism of the anesthesia process remains obscure, rational procedures in anesthesia are possible; yet anesthetists are often so dominated by traditional use of the empirical that they pass by opportunities for rational procedure. They have reached out and taken, for example, agents from the chemist and applied them hit or miss in anesthesia, disregarding the information available from the physiologist and pharmacologist and pathologist concerning these same substances, at the expense of lives. A search through the literature of anesthesia reveals little rational basis for much of it.

There is no need to labor the point that the achievements of modern medicine are greatly indebted to the laboratory. The only thing to remark is that here, at least until recently, an important division of medicine often disregarded it.

Fundamental Advances Have Rarely Been Made by Anesthetists. Too few of the chief workers in anesthesia have been creative in the sense of making fundamental contributions to the specialty. Anesthetists have developed and polished and increased the efficiency of processes discovered or created by those whose chief interests lie in other fields. Anesthesia has had to depend

upon casual contributions from other workers. These other men have provided the spark; anesthetists have, in the main, only fanned it. And herein, it seems to me, lies one of the most serious shortcomings of the specialty, a shortcoming that must be corrected before anesthesia can mature as a specialty. It is, surely, a great service to introduce advances from other fields into anesthesia. That is not the point. To live a vigorous life a specialty must have not only those who can apply the developments of others but also those who can create new ones. As long as its intellectual life is parasitic, the specialty will never develop satisfactorily.

ANESTHETIST AS INVESTIGATOR

The anesthetist may be a third-rate investigator or he may be a good one; but if his abilities and standards are high, he can be an invaluable associate of the professor of pharmacology. The final evaluation of all drugs used in man must be made in the clinic. The pharmacologist needs and ought to use his clinical associate quite as much as the other way around.

Well-established examples indicate that fundamental contributions in physiology are coming from new sources. Basic information is coming out of the clinic and at the hands of clinicians. I venture to say, as examples from my own hospital, that the contributions of Fuller Albright to the physiology of the endocrine glands are important, that Walter Bauer knows more about the physiology of the joints than anyone else. Human physiology turns out to be less comparable to that of the dog or the frog than some have supposed.

A few years ago a distinguished anesthetist, speaking in Boston, emphasized the importance of anesthetists sticking to the clinic and passing up any urges to do fundamental experimental work. These remarks of his were challenging, and coming from such a source, deserve consideration. But they ignore a trend in modern physiology: the shift of emphasis from animal physiology to human physiology, dependence where possible upon observations made in man rather than upon observations in animals. There are a number of problems that the well-trained, soundly grounded anesthetist is in a better position than almost anyone else to investigate, granting that he is not overwhelmed by routine work and that he possess the native ability and energy to do original work of good quality.

The physiologic response of man to drugs must often be tested out in hospitals where "basic" scientists rarely appear. If the trends of medicine show anything, they indicate that the anesthetist who heads a university's department ought to be capable of profiting by his opportunity to study man. In hardly any field of clinical medicine is such opportunity greater or its utilization more urgently needed than it is in anesthesia. Both basic scientist and clinician can make important contributions to the field of anesthesia. It is the obligation of the man who heads the university's department to do so.

The technical demands of surgery are so great that the successful surgeon will not often have adequate time to carry on investigation. It is one of the

great advantages of the field of anesthesia that the anesthetist can have such opportunity.

ANESTHETIST AS TEACHER*

Why should anesthetists completely relegate the basic instruction in their field to others (pharmacologists)? Is anesthesia so encumbered with difficulties, exacting technics, and demands against time that there is no opportunity for practitioners in this field to encompass the full demands of the specialty? If all responsibility for basic instruction in the field is given up, this will take away much of the intellectual interest and leave the technics. These alone will rarely attract the good man. Such action if embarked upon generally will give a disastrous blow to the specialty. It would be inaccurate to deny that this tendency is present; but isn't its very existence the result of too narrow a view of the field?

Is the university, then, to relinquish in the field of anesthesia all scholarly intent and say, in effect, bring on your technical specialty, admitting that in this division the university will give up its traditional ideals of scholarly workers in all of its parts and accept here a sort of trade-school level as the best it can do?

ANESTHETIST AS CLINICAL SPECIALIST

There is a clinical problem of compelling interest in this field. Most able men will not find it in the repeated application of clinical technics, but in applied pharmacology, in the hazards and rewards of translating material from the basic sciences into clinical use. To succeed in this sensibly and safely requires insight and judgment. Clinical anesthesia offers a continuing interest of this kind.

Anesthetists must assume wider burdens than those of clinical anesthesia in its specific sense: The treatment of shock, resuscitation (and this includes aspiration bronchoscopy), certain problems of aviation medicine, gas therapy of various kinds, sedation; these are all reasonable clinical fields for the anesthetist. Anesthetists can be the physiologically-minded guides of therapy in preparation for, during, and immediately following the rigors of surgical intervention. A broad medical background is indispensable for this, as for leadership in other fields. The importance of this essential background is often unwisely minimized by anesthetists.

The act of surgery is a complicated thing, influenced by knowledge and judgment, of course, and by various physical elements—hemostasis, asepsis, anesthesia. Whether anesthesia is or ever shall be a distinct specialty interests me very little. This is by no means a casual dismissal of the importance of anesthesia; it is an affirmation that *clinical* anesthesia is an integral part of

* Details concerning teaching are discussed in the following section on the "Harvard University—Massachusetts General Hospital Department of Anesthesia."

surgery, as inseparable from it as hemostasis. If one accepts this view, it seems to me that what validity there is in the claims of anesthesia to being a separate specialty lies in its administrative requirements and in its teaching and developmental aspects, more than in its clinical applications. To relinquish the teaching and developmental, as some do, is to leave little but the technical. If anesthesia is to be a specialty, then it must encompass all of these things. Herein, of course, lies the great vulnerability of anesthesia as a separate discipline. Unless its base is broad enough to include these things, its separateness as a specialty may collapse, for if limited to its clinical activities alone, it will rarely attract the good men who are essential to its development as a specialty. I emphasize again that such a concept does not minimize in the least the importance of anesthesia.

This concept has the not inconsiderable advantage of emphasizing a point too often lost sight of by the anesthetist: That he is a physician engaged in the practice of medicine, not a free agent rattling around in an isolated domain. Too often the anesthetist becomes so preoccupied with the technics and tools of his field that he loses his interest in medicine and whatever knowledge he had of it.

There is a tendency to permit the anesthetist to become established as a "specialist" without the broad apprenticeship of general hospital training in medicine or surgery required of *all* other men who look forward to activity as specialists. It is difficult to see how any man can claim to be a sound specialist in any field of medicine without this essential foundation.

ANESTHESIA IS AT ONCE SIMPLE AND COMPLEX

The very ease with which the simplest forms of clinical anesthesia can be administered has until recent years allowed almost the entire specialty in this country to rest in the hands of nurses, or physicians whose equipment is mainly limited to the technical, individuals who could not be expected to make advances. This statement is in no way intended to reflect upon their faithful and in many cases competent services in allaying pain; but so far as I know, no nurse has ever made a single contribution to anesthesia. In the hands of nurses, and in the hands of many physicians as well, anesthesia is a craft, a craft often beautifully perfected in some of its aspects, but not the part of medicine it might be. (The nurse anesthetist will be considered further, under the hospital's department.)

On the other hand, the first-rank problems of anesthesia are as fundamental, and as difficult, as any in medicine. The anesthesia process is inextricably bound up with irritability of tissue, one of the most fundamental characteristics of life. As Lillie pointed out years ago, the problem of the general nature of anesthesia is inseparable from the wider problem of the nature and conditions of irritability in general. Anesthesia, in its influence on cellular tissue, on the nervous system, provides an excellent tool for study of many physical and mental processes.

ANESTHESIA

THE FUTURE

Some departments of hospitals carry a great burden of routine technical procedures. Examples are the departments of pathology, roentgenology, anesthesia. The routine work on these services cannot be cared for by volunteers as on the medical or surgical services where the volunteers' rewards are great. Insofar as one can look into the future, it seems probable that active *university* hospital departments of pathology and roentgenology and anesthesia will contain two distinctly different groups of men working side by side.

Men in one group will be attracted and held by large salaries, for which they will give up leisure and freedom of activity in their specialty. Men in this group will carry the burden of hospital routine in their respective fields. (Some of these men will also be valuable as teachers.)

In the other group men will have, ideally, freedom from routine duties, freedom to pursue whatever investigations they wish, with only enough routine work to keep serviceable their already mastered clinical technics. (This is essential if they are to speak with authority on clinical matters.) Their recompense will be not in salary, which will be low, at least during their developmental period, but their reward will come in freedom from overwhelming routine duties, in an environment where they can grow in intellectual stature and in academic achievement.

Unless anesthesia is taught in terms of principles, it can hardly rise above the status of a craft. The university cannot be expected to foster anesthesia based upon the standards of the clinic alone. Anesthesia must develop scholarly aims and standards, characteristics, of university caliber before it can expect the patronage of the university.

Great efforts are being made at this time to increase the prestige of anesthesia as a specialty; how successful these will be remains to be seen. Certainly, present accomplishments must be and will be more widely distributed in the future than at present. I am not speaking of this aspect. The present efforts to develop anesthesia as a specialty are too limited, so far, to improving the clinical side alone. Truly this has needed and still needs improvement. There can be no question about this. The efforts that are being made are of great importance, as far as they go. But a specialty that has poverty of intellectual interest can scarcely become mature. How can any field that leaves nothing for the imagination to dwell upon expect any but the dullest candidates? To attract good students, a specialty must offer more challenging matters than those dealing with judgment and technic alone, indispensable as these are to the conduct of good clinical work. Opportunities for intellectual adventures must be presented. Such opportunities are abundant in anesthesia. They need exploration.

II. THE HARVARD UNIVERSITY-MASSACHUSETTS GENERAL HOSPITAL DEPARTMENT OF ANESTHESIA

Probably no two departments of anesthesia are or should be alike; but from the inquiries that are made concerning the principles and details of

organization of this one, an account of it may be useful, since it differs in many respects from the traditional. In several instances views that have been already expressed in the preceding section will be referred to here, even summarized briefly for clarity and for emphasis in the new context of this section.

PURPOSES

The Chief of the Department, as a Professor in Harvard University, has the obligation to teach and to do original work. As the Director of a Hospital Department he must provide the best possible anesthesia for the Hospital and carry on postgraduate training in clinical anesthesia. These fourfold activities will be discussed in detail; so also will the financial arrangements that make them possible. But first the principles that underlie the organization will be described. (There is some inevitable overlapping in the four categories mentioned.)

PRINCIPLES AND DETAILS RELATED TO INVESTIGATION IN THE UNIVERSITY'S DEPARTMENT OF ANESTHESIA

1. A great opportunity is afforded there to carry on studies in human pharmacology. A close association between the Professor of Anesthesia and the Professor of Pharmacology is desirable and an advantage to both. This should lead, not only to original work of distinction, but also to smooth clinical application of pharmacological and other basic advances. This requires judgment and insight of a high order. A close association between the clinic and the laboratory is essential if progress is to come.

2. It is the obligation of the University to choose as Professor of Anesthesia a man who is capable of doing original work of high quality. He must be provided with the time and equipment for work, and freedom from engulfing routine.

3. The chief intellectual stimulus in the field of anesthesia comes from investigation. For this reason, since a real intellectual challenge is necessary to attract good men, it is more important that the Professor of Anesthesia have the opportunity to carry on research than it is, say, for the Professor of Surgery. (The field of surgery is rich in resources and can attract good men for many reasons.) The chief hope of attracting good men to anesthesia as well as hope for growth of the field lies in investigation.

4. Anesthesia, in being relatively simple technically, fails to attract good men on this basis and is at the same time so baffling in its scientific aspects, as far as the mechanism of anesthesia goes that this also discourages good men. The only solution to this is further investigation. Anesthesia must attract those who are capable of original work, if it is to mature.

5. It is neither necessary nor desirable that all residents in anesthesia carry on so-called research. It is not only desirable but necessary that those

who are being fitted for an academic career do so. This presupposes that such men will have a flair for it.

6. Nurses have not contributed and cannot be expected to contribute to the development of anesthesia. (They work at a purely technical level; but so also do physicians who limit their interests to technics.)

PRINCIPLES AND DETAILS RELATED TO ACADEMIC TEACHING

1. It is desirable for the Professor of Anesthesia to lecture on the anesthetic agents in the medical school course in Pharmacology. He can thus stimulate the student's interest in the academic side of anesthesia in the second year of his medical course and can add clinical interest to this in the subsequent years of the student's training.

In the first three years of the medical course the student receives about 45 hours of instruction in anesthesia. This includes lectures, laboratory work, and firsthand administration of ether in the animal surgery courses. In the fourth year, weekly anesthesia discussion groups are held during the course in surgery. (Training of the student in clinical anesthesia on man is described in the following section on Clinical Teaching and Training.)

2. The Professor of Anesthesia must have available an abundance of clinical material for teaching and investigation and at the same time not be overwhelmed by routine clinical duties. Under our circumstances this requires that he function in the Medical School as a whole as far as teaching and research are concerned, but in *one* of the School Hospitals, as far as his clinical duties go, rather than in all. (This is customary at Harvard, and its counterpart can be seen in several departments; compare, for example, the Pathology Department.)

PRINCIPLES AND DETAILS RELATED TO CLINICAL TEACHING AND TRAINING

1. Anesthesia is not rich in technics, in the sense that surgery is. The technics of anesthesia are relatively simple. Probably few good men will ever be attracted to anesthesia by the technics alone.

2. The technics of anesthesia, like all medical procedures, are demanding in that even though once mastered they require constant application for continuing efficiency.

3. The technics of anesthesia require an apprenticeship type of training. Little is to be learned from observation alone; learning here, as in surgery, comes from doing. Therefore, it is necessary to provide an abundance of clinical material for use under guidance. Therefore, also, we struggle to avoid over-expansion of our training program, so that plenty of clinical material will be available for each man accepted for training. "Observers" are welcomed for a few days; a longer period passed in this way is probably a waste of their time.

4. Anesthesia technics must have a surer foundation than can be obtained in the clinic alone. It is important that they be taught in terms of principles first and details second.

5. The anesthetist should not be permitted to become a specialist without the broad clinical training in medicine required of other specialists in medicine.
6. Men are trained for Board of Anesthesiology certification.
7. Foreign students are accepted under rather stringent requirements. (See below.)
8. Interested medical students can take a month's course of fulltime training in anesthesia. All medical students administer at least ten open ether anesthetics. If they considerably exceed this number, they are taught to use nitrous oxide induction. All sit with and chart the course of five patients under local or spinal anesthesia.
9. It is desirable that house officers on the regular surgical service rotate through the anesthesia department, not to make anesthetists of them, but as a part of their surgical training so that they will understand the possibilities and limitations of anesthesia. Most house officers spend two months fulltime on the Anesthesia Service.
10. Nurses are trained to supply some needs. Nurses are permitted to administer only ether anesthesia (nitrous oxide induction), and this because of its well demonstrated factor of safety (respiratory failure gives drastic warning of overdosage with check of intake of the drug before any circulatory damage occurs). An equal factor of safety is not present with other anesthetic agents, and nurses are not permitted to administer them.

PRINCIPLES AND DETAILS RELATED TO HOSPITAL ORGANIZATION

1. The properly organized department of anesthesia should be self-supporting, and the department should pay its expenses (and it can if in the university hospital of average size about a quarter of the hospital beds are for private patients); but it should not make money. Legitimate expenses are: Salaries, supplies, equipment, a reasonable percentage payment for hospital overhead (bookkeeping, heating, light, janitor service, etc.) and a reasonable percentage of the income should be set aside for development of the department. The department will not remain static. It will go forward or backward; its continued development requires support. If the department continues to make money after these things are adequately provided for, fees should be lowered.
2. The Chief of the Department of Anesthesia must be free enough from routine obligations so that he can discharge the duties concerned with development of the department, teaching, and research. This means he must have able associates who can relieve him of much of the routine work.
3. The Hospital must provide the Professor of Anesthesia with abundant clinical material, for use as he needs it.
4. Oxygen therapy and most other gas therapy should come under the supervision of the Department of Anesthesia. Close interlocking arrangements with the Emergency Ward for resuscitation and with the Bronchoscopic Clinic for training of the anesthesia residents are necessary. The anesthetist

should have charge of fluid therapy during surgery. (When deterioration of the patient's condition occurs, the anesthetist informs the surgeon of it.) The anesthetist is an important member of various research groups in the hospital. He can lead at times, or follow at other times; but he is an integral part of investigation going on in the Hospital. The anesthetist must assume greater burdens than the clinical administration of anesthetic agents alone.

5. The able anesthetist who has spent as much time in preparing himself for his specialty as other members of the staff for theirs, deserves privileges and recompense equal to that of other staff members.

6. The costs of medical care are so great that anything that might cause them to rise (as, for example, the complete elimination of nurse anesthetists) must be examined with scrupulous care.

7. The final evaluation of drugs designed for use in man must in most cases be made in the clinic. The departmental organization must permit this. (See principles related to investigation.)

8. Anesthesia is as closely related to surgery as asepsis or hemostasis. Separation of anesthesia and surgery, except for administrative, teaching, and developmental purposes, is unwise and not to the patient's good.

9. Men in the good positions of anesthesia are more of the same age than is true in the other specialties. There is a great shortage now of anesthetists. In future years this may be considerably less acute than now and departments organized on the basis of free help may, in the years to come, be in trouble, it being harder then than now to get good men good jobs with the result that fewer men will seek anesthesia training then than now. (There will be many good opportunities again in 25 years.) The best anesthesia service can probably be provided by full-staff members with only a relatively few men in training, after the present great needs are filled.

10. Anesthetists are scarce, but even so the Anesthesia Department must be kept in balance in the Hospital as a whole; this chiefly concerns salaries, insofar as the great scarcity demand will permit.

DISCUSSION

In the preceding section on The Specialty of Anesthesia and in this section on Principles and Details, several of the items mentioned have either been discussed or do not need it. There are a few matters that perhaps need further elaboration. They will be taken up here.

The Professor and the Clinic. We have in this University the situation in which the Medical School is associated with several hospitals. This raises the question of how, in certain specialized fields where only one professor can be maintained, this professor ought to spread his effort.

When a professor requires a clinical post, as he does in a clinical field like anesthesia, it must be in one of the school hospitals. It cannot well be in all. While he can function as a consultant to all, routine duties in all would destroy his usefulness. The primary responsibility of a full professor must always be to the university. Although he may serve well the hospital where he

is situated, the hospital is never his home in the sense that the school is. The hospital is the sea in which he swims and from which he brings up such treasure as he can. The professor working in a clinical field dare not cut himself off from this clinical material. It must always be available. It contains the source material of whatever contribution he can make to medicine. The clinical material must not possess him, but he the material, as he needs it, on his own terms.

When a professor's seat is in one institution, that institution must, in return for this advantage, free the man from entangling hospital obligations by providing able associates, supported by the hospital, to manage most of the routine work. The establishment of a strong department in one school hospital will inevitably strengthen those in other hospitals. New attitudes, new procedures, new standards, new principles will emerge from the one that can be used by all. The hospital where the professor is, profits. All of the hospitals profit. And the professor has clinical material to use as he needs it. Unshackled by routine, he must be free to develop his department, to carry on the research and teaching that are his first responsibilities.

The teaching responsibilities interlock the Hospital and the Medical School, for teaching in this field has two sides: (a) basic science (Department of Pharmacology, at the Medical School) and (b) clinical (Department of Surgery, at the Massachusetts General Hospital and at the Medical School). A very satisfactory arrangement has been worked out with the Professor of Pharmacology whereby the Professor of Anesthesia lectures in that Department on the Pharmacology of the Anesthetic Agents. Acquaintance is made with the entire second class of the Medical School, and this acquaintance is developed by later lectures and clinics in the Department of Surgery, and finally in the third and fourth years by voluntary and elective courses in clinical anesthesia. The Professor of Anesthesia functions, then, in two departments of the School, but inseparably in the Hospital as well.

These arrangements for anesthesia have been put into operation in the Harvard Medical School and the Massachusetts General Hospital. Both sides have carefully supported the concepts described here.

The Department is robustly supported by the Hospital, both Trustees and Staff, supported to such an extent that in the present postwar reorganization we are constantly extending the service. In the beginning, the obstacles were great and progress difficult. But now an opposite condition exists: With the shortage of ably trained men so great, the danger is over-expansion.

The University Hospital can develop either of two types of anesthesia department: (a) There is the one that prides itself on, and indeed often achieves, a high degree of technical excellence, but limits itself to this. This type of department can be built up rather easily, depending on how willing the institution is to pay for it. Men to head such a department are not difficult to find. Beyond its technical services such a department will have little influence on the hospital or school as a whole, and none on the specialty. (b) The second type can have not only the goal of technical excellence, but also a profound interest in the foundations of the field, in improvements in it

of a basic kind, with a chief who will be considered as an equal by other departmental heads. Needless to say, such a man will be hard to find. Often the best solution for this problem is for the university to choose a young man who has the necessary qualities of mind and interest, and send him away for the necessary special anesthesia training.

Hospital Interns, Residents and Fellows. Hospital interns in surgery, while on the anesthesia service, and residents and fellows in anesthesia operate under the direction of the anesthetist according to the following plan: House officers in general surgery are assigned to Anesthesia for two months as a step in their training. Emphasis is placed upon observation of the behavior of patients subjected to anesthesia and surgery, with the aim of impressing upon these men early in their careers, not only the problems and limitations of anesthesia, but its possibilities as well, as a part of good surgical care.

The Anesthesia Department contains 20 physicians: Four of these are fulltime in research and the others fulltime in clinical anesthesia. There are 11 nurse anesthetists, with 9 in training.* A curriculum is provided for the training of physician anesthetists. A general internship of *at least* one year is required as a preliminary. Appointments are usually made for one or two years; but reappointments are made in suitable cases until the requirements are fulfilled for certification by the American Board of Anesthesiology.

In this course of training, increasing responsibility is given in the application of the various technics of anesthesia: Inhalation, intravenous, spinal, local and regional block. Training is provided in resuscitation, oxygen therapy and in bronchoscopy. Formal instruction is given in the pharmacology of anesthesia. Facilities are available for teaching and for basic and clinical research in the case of qualified individuals. Twice weekly, discussion groups and seminars are held. A close association with the Department of Surgery and the Department of Pharmacology of the Harvard Medical School is maintained.

Foreign students are carefully limited at the present time, owing to the great shortage of adequately trained men here. The occasional foreign student who is accepted for training comes on the following basis: For not less than one year, not more than two years. He must speak English well, and most important, he must be guaranteed a university teaching position to return to. Men who want training from even large foreign non-university hospitals are not accepted. We are convinced that these basic requirements help us to offer the most we can to foreign students and the lands from which they come.

Financial Arrangements. The anesthesia department in the usual type of university hospital where private as well as ward patients are admitted, can be easily self-supporting.

In the present case about two-thirds of the Professor's salary comes from the University and one-third from the Hospital.

* Agitated discussion concerning nurse anesthetists is rarely heard in this Hospital. In about a dozen years the Massachusetts General Hospital has progressed from no physicians in anesthesia to 20 with maintenance of a group of nurses.

Charges to private patients for anesthesia are made so that with the lower surgical fees, the anesthesia charge is about 15 per cent of the surgical, and in the case of the higher surgical fees, about 10 per cent. The anesthetist is usually closer to the patient than the pathologist or roentgenologist. Possibly work by men in these two fields can be established on a set fee basis. Anesthesia charges should, like those of the surgeon, be scaled to the patient's ability to pay. This is arranged by placing the charges for anesthesia at a fixed percentage of those for surgery. However, in the case of ward patients, fixed anesthesia charges are made as follows: Five dollars for the first two hours, \$7.50 for three hours, and \$10 for procedures that last over three hours.

With the great shortage of physicians trained in anesthesia at the present time, an acute problem is to keep the income of anesthetists in proper balance with that of other physicians working in the hospital. The Chief of the Department can take an all-out partisan view and get all he can for the Anesthesia Department, without regard for the remainder of the Hospital's staff, since Anesthesia is an easy earner. Or he can try to keep a balance with the whole hospital. Or he can steer a middle course between these two approaches, since he will hardly be able to defy the law of supply and demand.

DISCUSSION.—DR. FRANK H. LAHEY, Boston: It would be wrong for this paper to go undiscussed because it is such a good paper and such an important subject. Even if approached from a more utilitarian point of view than that of the author, it is still an urgent subject and one that has been neglected by the universities. Interest in anesthesia until recently has been evidenced largely by those who have been dealing with the subject from a clinical point of view and we are now observing an interest from the investigative viewpoint, which will round out the subject as it should be.

Over the years we have been greatly interested in the problem of anesthesia because it is so closely related to our surgical problems. We have run a school of anesthesia for a number of years, except during the period of the war when practically all the men in this school were being trained for anesthesia in the Navy, 41 being made available for Navy service. This has been a two-year period of training and, when the men have completed it, they are capable of heading a department of anesthesia in any medical school or any hospital.

Up to the time of the war I feel certain there had been a great lack of appreciation of the value of a trained physician-anesthetist. Because so many surgeons were able to have trained physician-anesthetists in the war, this has been largely overcome. Prior to the war we had difficulty in placing the men whom we had trained in anesthesia in suitable positions but we now have a demand which far exceeds the number we can supply.

Trained anesthetists can supply so much today that it is of interest to enumerate what they should be able to do. They should be able to grade the risk. They should be able to advise surgeons in consultation as to the most desirable type of anesthesia for a particular operation. They often can make suggestions in a given problem case which will be of distinct value in the management of surgical procedure. They should be able to take complete charge of the patient's care on the table, which has been such a heavy responsibility up to recent years for an operating surgeon already seriously burdened with responsibility. They should be completely responsible for transfusions; with so many patients today requiring and receiving transfusions while under anesthesia—at which time the early symptoms of improper matching cannot be appreciated—this is a real responsibility since they are responsible also for the accuracy of blood matching. They will save cardiac patients in cardiac arrest at the time of operation. We have had twelve patients

ANESTHESIA

with cardiac arrest (two of these had carotid sinus syndrome), of whom we have saved four with no subsequent cerebral damage. The heart was started in every case of the twelve, but too late to avoid cerebral changes in eight. Dr. Hamilton Bailey has recently reported an experience with 40 cases of cardiac arrest. The responsibility to restore cardiac action in patients with cardiac arrest is completely in the hands of the anesthetist, since he will be the one who first discovers it, and his acuteness and promptness in this respect will settle whether or not the patient lives. The anesthetist will be the one who will deal with carotid sinus reflexes, of which we have had several instances. One has to have only a few such cases to realize how hair-raising they are. The anesthetist will be responsible for shock; he will not permit the patient's blood pressure to drop and remain low over any period of time. In the early days before we had such good anesthesia and also improved surgery, our patients after operations of major magnitude usually left the table cold, blue and wet. Today, as a result of the excellent care competent anesthetists provide for them on the table, together with good anesthesia, and in spite of very extensive procedures, they now leave the operating room warm, dry and pink. This is purely the result of the responsibility for their condition being in the hands of the anesthetists. They should be able to provide diagnostic blocks. They should be able to do bronchoscopies, to handle 100 per cent oxygen, helium, and any number of things that only add emphasis to what I have already stated.

As to the supply side of the problem, there are not and will not be enough professional anesthetists to go around unless we do more than we are doing in training anesthetists in the various hospitals. Every hospital that takes on a professional anesthetist has, in my opinion, a serious obligation to see that he, in turn, is training other anesthetists.

As to the effect of this expert anesthesia upon surgery itself, I have repeatedly said that in my opinion it has definitely decreased the morbidity and mortality, and I would like to emphasize further that a good professional anesthetist will lower the morbidity and mortality in the surgeons themselves.

DR. ALFRED BLALOCK, Baltimore: I rise mainly to express my admiration for the author of this paper and the guest of this Association, Dr. Beecher. His work in the field of anesthesia has done much to advance this subject. He is a leader in research, in the teaching of students and in the training of anesthetists. Dr. Beecher does not advocate that anesthesia be divorced from surgery. In fact, he states that anesthesia and surgery are bound to each other as are surgery and hemostasis.

I am alarmed by the present tendency of some to discredit the ability of the nurse-anesthetist. All of us must be aware of the damage that may result from articles in the public press to the effect that it is unsafe to be operated upon in a hospital which is not staffed solely by physician-anesthetists. Furthermore, is it proper to maintain that the nurse anesthetist is only a technician? There are hundreds of hospitals in this country in which major surgery is performed and the number of M.D. anesthetists is totally inadequate to staff these. Even if it is desirable that these positions should be filled only by physicians, I doubt seriously if this field of work will attract physicians in sufficient numbers to supply the need within the next few decades. Conversations with a number of physician-anesthetists lead me to believe that many of them deplore the present inclination of some members of the profession to underrate the ability and the worth of the well-trained nurse-anesthetists. Many of these have exceptional qualifications. For example, Miss Olive Berger has anesthetized the last 225 patients upon whom I have operated for congenital heart disease, and my associates and I have the highest regard for her ability.

We are fortunate in having heard Dr. Beecher, whose general ideas regarding the field of anesthesia are sound and commendable.

GRADUATE TRAINING IN SURGERY IN VETERANS ADMINISTRATION HOSPITALS*

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THE RETURN FROM MILITARY SERVICE to civilian life of many thousands of medical officers whose training was interrupted by the war and who desired to complete specialty qualifications created a problem far beyond the scope of existing graduate educational facilities. The medical care of veterans of both World Wars in facilities which had been inadequate to meet the needs of World War I alone, created a problem for the Veterans Administration which would have been insurmountable under former methods of administration. Under the direction of General Omar Bradley, the reorganization of the Veterans Administration hospital program by Dr. Paul Hawley, with the assistance of Dr. Paul Magnuson, has progressed far beyond expectations in meeting these two problems. The prime purpose of their program is to offer the best available medical care to men and women who have served their country in the Armed Forces. Any program which would not fulfill this purpose would not be justifiable. Yet facilities and personnel available to them when they assumed their present responsibilities were so inadequate to meet the needs of veterans of World War I alone that most existing hospitals had long waiting lists and an insufficient number of physicians to render prompt medical care. They knew that existing opportunities in the Veterans Administration would not attract the number of competent doctors required to meet the expanding needs. Their vision in enlisting the aid of medical schools has to a large extent solved these problems. It has made available to the veteran patient the faculties of participating medical schools and thus some of the finest medical talent in the country. It has given to the most promising veteran medical officers an opportunity to complete their training and at the same time render valuable medical care to men who have become afflicted with disease during or subsequent to military service.

Briefly, the professional care of patients in veterans' facilities located near universities has been placed under the supervision of medical schools able and willing to participate in the program. Committees composed of deans of these schools have assumed responsibility for the successful accomplishment of these aims. The wholehearted support of medical schools throughout the country is shown by the following table enumerating the number of such programs now in operation.

* Read before the American Surgical Association, March 25, 1947, Hot Springs, Va.

† Deputy Chief, Surgical Service, Veterans Administration Hospital, Hines, Illinois.

GRADUATE SURGICAL TRAINING

TABLE I

VETERANS ADMINISTRATION RESIDENCY TRAINING PROGRAMS (as of February 1, 1947)

Medical schools participating.....	55
Deans' Committees Supervising.....	33
VA hospitals and clinics utilized.....	58
Residents in training.....	1,635

Good civilian hospitals long have recognized the importance of internes, residents or both in rendering the best professional care to patients. All teaching and superior private or municipally administered hospitals depend upon an adequate house staff to maintain high professional standards. By establishing residencies in Veterans Administration hospitals, nearly 2,000 competent young physicians are now helping to meet the demands of the veteran patient and at the same time are furthering their training under supervision of the country's best medical educators. Many of these men, who otherwise would not have been attracted to this service, will make a life work of it and assure continued good care in Veterans Administration hospitals.

As the specialty boards have set up standards recognized as essential to the training of qualified specialists, their requirements have been used as the basis for resident training programs established by the Deans' Committees and the Veterans Administration. In spite of the short time that has elapsed since these programs have been introduced, many already have been approved and many more are awaiting inspection.

TABLE II

SPECIALTY TRAINING PROGRAMS IN VETERANS ADMINISTRATION HOSPITALS

Approved by Council on Medical Education and Licensure of the American Medical

Association.....	52
Applications for approval.....	129
Approved by the American College of Surgeons.....	59
(Many awaiting inspection for approval)	

One of the first Deans' Committee programs was instituted at the Veterans Administration Hospital at Hines, Illinois, under supervision of the Colleges of Medicine of Northwestern University and the University of Illinois. This program will be discussed somewhat in detail to exemplify what has been established and what has been accomplished in the first year under the present administration. Although Vaughan General Hospital, formerly administered by the Army Medical Corps, has been utilized as an addition to the Veterans Hospital, almost its entire capacity is being used for the care of paraplegic, tuberculous, psychiatric and neurologic patients. After the reduction of overcrowding by the elimination of hundreds of emergency beds, the actual capacity for general medical and surgical patients at Hines has been

TABLE III

ADMISSIONS TO VETERANS ADMINISTRATION HOSPITAL, HINES, ILLINOIS

Total		Monthly Average	
1945.....	11,118	1945.....	926
1946.....	17,748	1946.....	1,479

increased by less than two hundred beds. Thus the increase in patient admissions is far greater than would be expected from the increase in bed capacity.

This increase in admissions is due largely to an acceleration in the care of patients enabled by a more adequate professional staff. The former staff worked efficiently but was so inadequate in number that it could not maintain a rapid turnover of patients. Many bottlenecks existed because of insufficient equipment and personnel. Many of these have been corrected but others still exist which must be eliminated before the hospital can function at maximum efficiency. When contemplated changes are completed, each hospital bed will serve at least twice the number of patients it formerly did. The greatest present handicap is a shortage of operating rooms. Only five operating rooms are now available to serve nearly a thousand surgical beds. As a result, the hospital stay of many patients is prolonged by at least one to two weeks awaiting operating facilities. In spite of this, the admission of surgical patients has been nearly doubled.

TABLE IV

ADMISSIONS TO SURGICAL SERVICE VETERANS ADMINISTRATION HOSPITAL, HINES, ILLINOIS

	1945	1946
General Surgery.....	1,250	4,130
Tumor Service.....	2,344	2,359
Orthopedic Surgery.....	637	1,401
Urology.....	697	1,184
Women's Surgery.....	227	286
Eye, ear, nose and throat.....	537	1,289
Total.....	5,692	10,649

By utilizing the operating rooms both morning and afternoon on a closely integrated schedule, the number of surgical procedures performed in the existing facilities has now greatly increased.

TABLE V

OPERATIONS PERFORMED AT VETERANS ADMINISTRATION HOSPITAL, HINES, ILLINOIS

Specialty	1945	1946	Increase	%
General Surgery.....	2,391	3,829	1,438	60
Orthopedic Surgery.....	337	699	362	107
Plastic Surgery.....	214	457	243	114
Urologic surgery.....	471	884	413	88
Vascular surgery.....	206	343	137	67
Thoracic surgery.....	279	375	96	34
Neurosurgery.....	87	318	231	265
Total.....	3,985	6,905	2,920	73%

However, no attending surgeon can be permitted to operate more than two half days per week because of this shortage of space. Plans are completed to construct more operating rooms which should increase the surgical output by at least 50 per cent. A separate operating room exists for the ophthalmologic and otolaryngologic services. These have been active services in the

GRADUATE SURGICAL TRAINING

past, but their reorganization has been considerably delayed. Operations performed on these services are as follows:

	1945	1946	Increase	%
Ophthalmology.....	141	284	143	101
Otolaryngology.....	1,083	1,140	57	5

An additional operating room has been completed for these specialties and its benefits are being reflected in their present output.

PROFESSIONAL STAFF OF VETERANS ADMINISTRATION HOSPITALS

Four categories of physicians now serve the veteran patient. They are

1. Consultants
2. Attending physicians and surgeons
3. Full time Veterans Administration physicians
4. Residents

The consultants are outstanding specialists whose services are sought when professional problems arise which cannot adequately be met by the attending staff. They also serve in an advisory capacity in the administration of many special departments. The attending physicians and surgeons are responsible for the professional care of a great majority of veteran patients. These men spend an average of five half days per week in carrying out their duties. They must be veterans of World War II, faculty members of a sponsoring university, and must be certified by a specialty board or have equivalent training. A few full-time Veterans Administration physicians are included on the professional staff of some of the Deans' Committee hospitals. Their services are very valuable in handling the administrative work required by the Veterans Administration and in helping to maintain satisfactory function of the various departments. Thus far all residents are veterans who have been in active service during World War II. As internes are not utilized at present, it is the resident's responsibility to take case histories and physical examinations and to request all necessary special studies demanded for an accurate diagnosis. On the surgical services, they are responsible for the pre- and postoperative care of patients assigned to them. They assist the attending surgeon at all operations and perform those operations under the direction of the attending surgeon which he believes them competent to perform. The residents are most important in the efficient functioning of the hospital's professional staff. The number appointed is determined by the hospital's needs. It is our opinion that one resident cannot satisfactorily handle more than 20 to 40 patients, the number varying with the type of service to which he is assigned. In general surgery, one resident is responsible for 30 patients. In some of the specialties, a smaller number of patients is assigned to each man, whereas in others the number can be increased. However, in order to meet training requirements, it is necessary to assign residents to basic science studies and to other hospital functions. On the surgical service at Hines Hospital, an over-all ratio of one resident to 18

patients has enabled us to meet hospital requirements and training needs. At present we have 144 residents who are distributed as follows:

TABLE VI

Internal medicine.....	44
Neurology.....	7
Psychiatry.....	6
Surgery.....	
General.....	41
Orthopedics.....	8
Urology.....	7
Thoracic.....	3
Neurosurgery.....	4
Otolaryngology.....	4
Ophthalmology.....	3
Anesthesiology.....	11
Radiology.....	6
Total.....	144

RESIDENT TRAINING PROGRAM

The requirements for resident training have been fairly well established by the specialty boards. These requirements, with some modification, are used as our criteria for our own training program. A few principles have been incorporated by the Deans' Committee to somewhat amplify this program. They believe that a man trained in any surgical specialty must have a broad foundation in the principles of general surgery and in the basic sciences. For this reason, men being trained in surgical specialties are required to spend six months on the pathologic service where they are trained in both pathology and in surgical anatomy. From six to 18 months are spent on general surgical services. After completion of this training, the men then are assigned to services in their own chosen field.

Likewise, it is believed that some knowledge of surgical specialties is important to the development of a competent general surgeon. Although the program varies to some degree with the desires of the individual resident, the following outline includes those services through which most general surgical residents rotate.

TABLE VII

PROGRAM FOR GENERAL SURGICAL RESIDENTS

	Months
Admitting service and night surgery.....	3
Tumor diagnosis and therapy.....	3
Surgical specialties (four of 3 months each).....	12
General surgery.....	12 to 18
Pathology and anatomy.....	6
Other basic sciences throughout entire residency	

Admitting Service. When the Deans' Committee assumed responsibility for the professional care of patients at the Veterans Administration Hospital, Hines, Illinois, a survey was made to determine how many hospitalized patients actually needed hospital care. It was found that nearly 40 per cent of patients in the hospital could be treated satisfactorily as outpatients or could not be benefited by further hospitalization. These patients occupied a

sufficient number of beds to make it impossible for existing facilities to meet the veteran hospital needs of the community. At that time, admissions to the hospital were accomplished by full-time physicians who did not participate in the professional care of patients and who were less concerned with the dangers of overcrowding and with the ability of the hospital to meet the demands placed upon it than were physicians who were actually serving in the hospital. As a result a waiting list of nearly 2,000 patients existed in the early part of 1946. This included veterans suffering with malignant disease upon whom action had been deferred for several months. Many patients upon whom elective surgery was indicated were required to wait as long as one year before they could be hospitalized. This often meant prolonged unemployment if correctible diseases prevented occupation. It was believed that more careful screening of patients for admission would enable the hospital better to meet the community demands. As the residents are competent to recognize disease and are conscientious in admitting only patients who need hospitalization, a number are assigned to the admitting service where they take histories and examine all patients applying for admission. If any question of doubt arises, consultation is called and utmost care is taken not to refuse hospitalization to any patient whom it would benefit. By the use of this system, although more than 50 per cent of people applying for hospital admission are rejected, we know of no instances where care has been denied to any patient needing hospitalization. This careful screening has not only enabled the hospital to meet the community needs but it has also entirely absorbed the waiting list, and all veterans applying for admission can be immediately admitted to the hospital when such service is needed. This is true in spite of the fact that the hospital is now serving not only World War I veterans but also those of World War II. During 1945, more than 90 per cent of hospitalized veterans had served in World War I. At present over 60 per cent of patients are veterans of World War II. This indicates that the number of veterans being served by the hospital has more than doubled. Thus by careful screening of patients and by nearly doubling hospital admissions, existing facilities are now serving a function three to four times as great as they did two years ago.

Each surgical resident spends six weeks on the admitting service. He is not assigned to this service until he is sufficiently familiar with hospital routine to understand the importance of his duties and is sufficiently trained to perform these duties in a highly satisfactory manner. While on this assignment the resident does not have actual operating room service but he receives experience in diagnosis which is important in the training of a surgeon.

Night Surgery. Because most Veterans Administration hospitals do not have facilities for housing residents and as many of them live at considerable distances from the hospital, it is impracticable for them to be subject to call both day and night. For this reason, a night service has been established to which each surgical resident is assigned for a period of six weeks. He is available for any calls on the surgical wards and for the care of emergency surgical admissions. A senior surgical resident is on night duty at all times to assure

competent surgical judgment. When he deems it advisable, he solicits the aid of an attending surgeon.

Tumor Diagnosis and Therapy. Training in the recognition and institution of proper therapy of malignant disease is essential to every surgeon. As nearly 2500 patients suffering from some form of cancer are admitted to the Veterans Administration Hospital, Hines, Illinois, an excellent opportunity for training in this field is available. Although patients with surgical tumors are assigned to the specialty in which field the lesion is located, all tumor patients are seen in consultation by the tumor service and are reviewed by the tumor board. After appropriate therapy and before discharge from the hospital, these patients again are presented before the tumor board. This vast experience is invaluable to the surgical residents who are assigned to the tumor service for a minimum of three months. As the chief of the tumor service is a well-trained oncologist and has had special training in surgery for malignant disease of the head and neck, the surgical ward for such lesions is a part of the tumor service. Non-surgical tumors which are treated by radiation also are hospitalized on this service. Although it is not our desire to train surgical residents to become radiologists, we believe it important for them to be cognizant of the possibilities of this form of therapy.

Basic Sciences. Considerable controversy exists as to whether basic sciences, particularly pathology and anatomy, should be taught on a full-time basis covering a period of weeks or months or should be incorporated with clinical teaching throughout the residency period. Theoretically, the latter has some advantages. However, experience has shown that residents on active clinical services frequently do not allow sufficient time for basic science study. Because of the excellent teachers and the amount of material available to us in the basic sciences, we have adopted the policy of assigning each surgical resident to the pathologic service for a period of six months. The comprehensive course of lectures by the chief pathologist and attending pathologists from the faculties of the sponsoring medical colleges provides excellent training in the study of abnormal tissues. The large number of surgical specimens and the great amount of necropsy material offer unusual teaching opportunities. During this period of six months, surgical anatomy is taught on available material by an anatomist who is also certified by the American Board of Surgery and who lectures and demonstrates from a surgical viewpoint. Sufficient time is available to the resident during this six months' assignment for him to complete or become well established upon a clinical or pathologic research problem. Excellent library facilities are at his disposal to encourage complete review of pertinent literature. Other basic sciences, particularly bacteriology, physiology and bio-chemistry are taught at weekly conferences throughout the entire residency. In these conferences stress is laid upon the clinical application of the basic sciences.

ALLIED SPECIALTIES

Roentgenology. In order to give surgical residents a better understanding of roentgenology, weekly conferences are held in this subject. In addition to

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this, the staff and consulting radiologists are available at all times to review with the residents roentgenograms and fluoroscopic studies of their patients.

Anesthesiology. The department of anesthesiology is administered as a subdivision of the department of surgery. Only graduate physicians are used as anesthetists. Four physicians certified by the American Board of Anesthesiology supervise the work of 12 residents in this department. The residents in anesthesiology examine all patients prior to operation and cooperate on pre-operative orders and the selection of anesthetic agents. They are equally responsible with the surgical resident for the care of postoperative complications, especially those which may in any way be related to the anesthetic agent employed. Although surgical residents are not employed at present in the department of anesthesiology, it is believed that some knowledge in this field would be of benefit to them in their future careers as surgeons.

SUMMARY

The Veterans Administration hospitals will be called upon to serve 15 to 20 million former members of the armed forces. This is four times as great a number as they served prior to World War II. Although expansion of existing hospitals and construction of new ones will be necessary and are contemplated to meet this demand, it will be many years before such construction can be completed. It has been shown that by proper administration and with adequate personnel, existing hospital facilities of the Veterans Administration can serve a far greater purpose than they have in the past. They not only can offer better and more extensive medical care to the veteran patient, but can provide excellent graduate training facilities for the returned medical officer. The Veterans Administration has solicited the aid of the medical schools of this country to help in this program. It is the responsibility of the participating Deans' Committees to so organize the professional services of the hospitals that they will render the best possible professional service to the veteran patient and offer the greatest possible training opportunities in the surgical specialties. It is also their responsibility to the taxpayers of the country to supervise the professional care in these hospitals in such a manner that undue expansion will not be necessitated by inefficient administration.

DISCUSSION.—DR. PAUL B. MAGNUSON, Chicago: The medical profession has supported this program from the start and I think has accomplished something never before even dreamed of in any country. We did not know when we started what co-operation we would have from the medical profession, and I doubt that we would have had this whole-hearted support had not General Bradley and General Hawley authorized the plan to set up Veterans Hospitals on the basis of mutual advantage. This advantage, I believe, is apparent to all who are teaching.

In the first place, we had to take care of the veteran patient. Second, we were under obligation to provide the veteran physician with further training in view of his having been called away from training to serve in the armed forces. The 1600 Residences created in about a year are serving to continue training for those men whose careers were interrupted by the war. These Residents have been paid more than will be the case in the future when Residents will not be veterans. The sum of \$3300 is a lot to pay a Resident, but the Senior Resident's pay of \$1800 was supplemented, because under the Bill of

Rights these men were entitled to up to \$500 per year for educational purposes, plus \$65 per month if single and \$90 if married, for subsistence. Taking into consideration the fact that they were all older men, many of them married, it was felt that they were entitled to a greater compensation on their return from service; therefore their pay was placed at a higher figure than it will be in the future.

We also owed another debt to men coming back from service, men well trained and working in universities, who were called into service before they had the opportunity to become established; men coming back who had neither offices nor practices. By offering the schools the advantage of putting these men in part time positions, giving service to veterans at a reasonable compensation while building up their practices, we helped that group.

The older group, most of us, stayed home; we were too old or too decrepit to go into the army, according to General Kirk's standards. This group, largely men of professorial rank, has guided the program through with the assistance of the Deans' Committees of all the medical schools. The Deans' Committees chose to act without compensation because by so doing they would not be under pressure from any source. This has been of mutual advantage, for this reason. The promising young men as they finish their Residencies can retain affiliation with the medical school, can be put on as attending men at Veterans Hospitals, and at the same time can continue with research and laboratory work until such time as the medical school decides whether or not they want them on the faculty. Most medical schools do not have the funds to retain such men at any stipend.

Most of the new hospitals will be built on the campuses of universities. They will not be domiciliary hospitals; they will be hospitals for acute care. Fort Snelling at Minneapolis cut the hospital stay from 42 bed days per patient to 19 bed days per patient, and I think that would compare favorably with most civilian hospitals.

The medical profession must retain control of this program or, as Dr. Puestow said, it will go back into the same old hands. We must have strong men, not only in the hospitals controlled by the Deans' Committees but in Washington and in the various districts. It is up to the medical profession to hold the ball, now that they have it, and run with it. If we do not—well, politicians and bureaucrats live on for ever!

DR. EDWARD D. CHURCHILL, Boston: I should like to ask Dr. Magnuson why, if this group of young men is going to save the country thirty billion dollars and carry this work load—why decrease their salaries?

DR. PAUL B. MAGNUSON, Chicago: If we were to go into a city where the ordinary stipend of a Resident is \$1200 a year, and offered \$1800, \$2400, \$3000, we would be putting our Residencies in competition with Residencies in universities that are assisting in this training program. We do not intend to put the same value on service in communities where it costs fifty cents on the dollar to live—if any such exist—in comparison with cities where the expenses are much higher. The cost of living in a small community is much less than in Chicago or New York, or the other robber baron eastern cities. We feel compensation for Residents in the Veterans Administration should be equalized with that of civilian hospitals. Certainly we did not want to put these Residency appointments on a competitive basis of money alone, because we might get Residents who were more interested in dollars and cents than in the training offered. Therefore, in the future they will be offered the same compensation as is prevalent locally, according to their grade—junior, intermediate or senior.

TOXOID IMMUNIZATION IN EXPERIMENTAL GAS GANGRENE*

A Preliminary Report

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THUS FAR EFFECTIVE PROPHYLAXIS in gas gangrene has been limited to early and adequate surgery.¹⁻⁹ Recently penicillin, administered parenterally,¹⁰ has been shown to be a very valuable therapeutic adjunct to surgery. Its prophylactic effect was greatest when it was used early and in massive doses and consisted of a limitation of the rate of spread and extensiveness of the infectious process as well as a marked retardation in the rate of death.

The possibility of producing active and effective immunity for this infection has been explored in recent years, since various powerful exotoxins generated by the clostridia play an important role in the pathogenesis and toxemia of gas gangrene. Kolmer¹¹ studied the immunizing capacity of the toxoids of *Cl. welchii*, *Cl. septicum*, and *Cl. oedematiens* in guinea pigs and concluded that the degree of acquired immunity was much less than that produced by tetanus toxoid. Stewart¹² also investigated the effect of two injections of *Cl. welchii* toxoid in guinea pigs and found that the animals which developed titers of 0.25 or more units of antitoxin per cc. showed marked resistance to intramuscular inoculations of either toxin or virulent cultures. Robertson and Keppie¹³ confirmed the observations of Stewart on serum antitoxin levels necessary for protection against lethal doses of bacteria. Dowdy¹⁴ working with single doses of *Cl. welchii* toxoid in dogs, reported in 1945 that 0.1 unit per cc. of serum of alpha antitoxin was the critical level determining the survival of dogs challenged with intramuscular injections of virulent cultures. In a group of 23 dogs with serum titers less than 0.1 unit per cc. there was a 43.5 per cent survival rate, whereas in a group of 51 dogs with serum titers of more than 0.1 unit of antitoxin per cc., there was a survival of 96 per cent. When he gave an additional or booster dose of toxoid, he obtained a marked increase in the serum antitoxin titer and a survival rate of 100 per cent.

Logan and Tytell¹⁵ compared data on the immunologic response of animals to various *Cl. welchii* toxoids and came to the same conclusions as Dowdy. They prepared an alum precipitated *Cl. welchii* toxoid which was found to be effective in producing a measurable and protective titer of antibodies in mice, guinea pigs, rabbits, pigeons, dogs, and humans. Good protection was obtained in the animals against multiple lethal doses of toxin and bacterial cultures injected into healthy muscle through fine needles.

* Read before the American Surgical Association, March 26, 1947, Hot Springs, Va.

These studies were very interesting but from a surgical point of view several criticisms became obvious. The experimental lesions produced by the injection of toxin or virulent bacteria into healthy muscle are vastly different from those of clinical gas gangrene, which are almost invariably associated with large areas of grossly contaminated and devitalized tissues, produced directly by trauma or indirectly by laceration or thrombosis of nutrient arteries. In addition, experimental gas gangrene produced by the simple injection of toxins or bacteria is much less severe^{10, 16} and more responsive to therapy than that produced in the presence of crushed muscle and dirt. Likewise, the use of local irritants such as calcium chloride along with the injected bacteria failed to produce as severe an infection. Furthermore, there is increasing evidence that the toxemia of gas gangrene is complex, being caused not only by the known bacterial exotoxins absorbed from the site of injury, but also by other factors, possibly arising from the septic degeneration of devitalized tissue. Consequently, it seemed probable that the immunity reported thus far in experimental animals injected with toxoid inadvertently has been made to appear greater than it really was. Finally, the inference that measurable amounts of antitoxin such as 0.1 to 0.25 units per cc. in the blood of patients or animals are necessarily synonymous with actual protection against a severe form of challenge or clinical infection has not been proved.

The problem of toxoid immunization against a more severe form of gas gangrene closely simulating the clinical type was undertaken in March 1945 through the combined efforts of the Departments of Surgery and Biological Chemistry of the University of Cincinnati, in an effort to evaluate fully the degree of immunity produced in experimental animals by injections of toxoid as advocated by Logan and Tytell, and to explore further the possibilities of effective immunity of experimental animals by other forms of toxoid prophylaxis.

MATERIAL

Guinea pigs were chosen as the experimental animal because of their marked susceptibility to *Cl. welchii* infections and their immunological response which resembles closely that of the human being. In addition, most of the earlier work was done with this animal. *Cl. welchii* was chosen as the test organism because of its occurrence alone or in association with other bacteria in 56 to 100 per cent of the cases of gas gangrene in a previously reported series.¹⁷ Strain BP6K was used and cultures of it which were grown in pancreatic digest media were characterized by prolific growth with much turbidity and gas formation and a higher degree of virulence than those grown in deep meat broth, brain broth, or other media. When incubated for only 4½ to 5½ hours in the pancreatic digest media, they produced death in much higher dilutions than when incubated 18 to 24 hours. Weekly passage through pigeons was necessary to maintain the virulence at a high level and this was done routinely by the Department of Biological Chemistry. It was therefore possible to maintain the virulence of a strain of *Cl. welchii* at a high level by incubating

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for 4½ to 5½ hours in pancreatic digest medium a culture of BP6K passed weekly through a pigeon. The *Cl. welchii* toxoid was produced from toxins of high potency and was made in large quantities by a reproducible procedure yielding many thousands of doses.¹⁸ Concentration and detoxification was accomplished by precipitation first with ammonium sulphate and then with alum.

METHOD

Sixteen groups of guinea pigs consisting of 17 to 29 animals each received two or three injections of the alum precipitated toxoid prepared by Logan's method at varying intervals and with varying doses (Table I). A total of 364 animals were injected with toxoid and compared with 274 controls.

TABLE I

Group	No. of Animals	Injection	Dose of Toxoid in Lb.	Time of Injections Before Challenge in Weeks	Per Cent Survival
7B	17	2	30-30	28-22	12
12A	24	2	30-30	4-2½	33
15	25	2	30-30	8-3	100
12B	23	3	30-30-30	10-7-4	63
13	23	2	30-30	8-3	56
14A	25	2	60-60	7-4	70
16A	25	3	40-40-40	22-10-1-3/7	95
16B	25	3	40-40-40	24-20-1-3/7	60
16C	24	3	40-40-40	26-22-1-6/7	50
16D	29	3	40-40-40	28-24-1-3/7	24
17A	25	3	60-60-30	13-9-1-3/7	23
17B	25	3	60-60-30	14-10-1-3/7	65
17D	15	3	60-60-30	16-12-3-3/7	46
17-DT	15	3	60-60-30	16-12-3-3/7	26
18A	21	2	60-60	5½-2½	28
19	23	2	120-120	4½-2½	52
Controls	274	1	00.0

Seven groups received a series of two injections and nine received three injections. The individual doses of toxoid varied between 30 to 120 Lbs. The injections were made subcutaneously at varying times in an effort to determine the optimum intervals between inoculations. After expiration of the selected period of immunization, the groups were challenged by a severe form of experimental gas gangrene produced by the following method:

The skin over the lower back, posterior and lateral aspects of the thigh of a guinea pig was prepared by shaving and scrubbing with soap and water for five minutes. After the induction of drop ether anesthesia, the preparation of the operative area was completed by the application of alcohol, ether, and tincture of iodine. A sterile drape containing a hole 1.5 by 1.0 cm. was then applied to the prepared area. These steps were necessary to eliminate or minimize the introduction of *Cl. welchii* spores normally resident on the skin or hair of the guinea pig.¹⁹ Under aseptic precautions using gown, gloves, cap and mask, an incision 1.0 cm. in length was made through the skin and sub-

* From the Department of Surgery, University of Cincinnati. The work described in this paper was done under contracts recommended by the Committee on Medical Research of the Office of Scientific Research and Development, the U. S. Public Health Service, and the U. S. Army.

cutaneous tissues over the mid portion of the postero-lateral aspect of the right thigh and developed down to and beyond the femur. The muscles on each side of the wound were then crushed five times with a Kocher clamp and then avulsed by twisting the clamp 180° . In each wound 0.5 cc. (0.6 Gm.) of an autoclaved and finely divided mixture of soil and cinders was placed. The edges of the wound were then closed with interrupted fine black silk sutures to minimize leakage of the inoculum and subsequent secondary contamination. In a previous series of experiments,¹⁶ it had been determined that the presence of crushed muscle and dirt increased the virulence of *Cl. welchii* 1,000,000 times. Serial dilutions of a $4\frac{1}{2}$ – $5\frac{1}{2}$ hour culture of *Cl. welchii* were then made to the tenth power using sterile pancreatic digest media as the diluent since it gave more uniform results than saline. Finally 0.5 cc. of one of the higher dilutions representing 1–100,000 minimum lethal doses was injected through the skin into the operative area containing crushed muscle and dirt by means of a 25-gauge needle and a tuberculin syringe. The minimum lethal dose was considered to be 0.5 cc. of the highest dilution of the culture which killed all of the guinea pigs within $4\frac{2}{3}$ days under the conditions of the experiment on a given day.

Since the minimum lethal dose varied between a dilution of 10^{-6} and 10^{-9} , it was found necessary to control carefully each experiment by a group of 25 animals which were used to determine the minimum lethal dose on the day of challenge and under the specified conditions. This was done by the injection of 0.5 cc. of serial dilutions of a $4\frac{1}{2}$ – $5\frac{1}{2}$ hour culture of *Cl. welchii* made to the tenth power from 10^{-5} to 10^{-9} . After challenge, the animals and their wounds were carefully observed over a $4\frac{2}{3}$ day period, and the date of death and extent of the lesion were determined in each instance. In this manner it was possible to determine the minimum lethal dose for each experiment and to measure the degree of immunity produced by the toxoid injections against a severe form of experimental gas gangrene resembling closely the clinical type. Determinations of the blood titers of alpha antitoxin were made in 4 to 8 representative animals in each group to determine any correlation between actual immunity and antitoxin levels. All surviving animals were observed for an additional ten days. No other form of therapy or prophylaxis was used in these experiments.

RESULTS

The degree of immunity obtained was found to vary between 12 per cent and 100 per cent, as measured by the rate and per cent of survival, depending on the number of injections, the size of the dose of toxoid, the interval between injections, and the severity of challenge.

When two injections of 30 Lbs. of *Cl. welchii* toxoid were given (Group 7B) seven months and $5\frac{1}{2}$ months before challenge with 10–10,000 MLD's of *Cl. welchii* culture, only 12 per cent of the animals survived the test period of $4\frac{2}{3}$ days and all of the animals died within six days with extensive lesions (Fig. 1 and 2). When the injections with the same dose of toxoid were

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made two months and three weeks before challenge (Group 15) with 1-10,000 MLDs, 100 per cent of the animals survived for nine days, and 64 per cent were still living 15 days after challenge. The lesions produced in this group of immunized animals were minimal or definitely less severe and extensive than those in the control group. When the period of immunization was further shortened giving the same dose of toxoid in two injections four weeks and 2½ weeks before similar challenge, the results were not as good and only 33 per cent of the animals survived the test period of 4⅔ days (Fig. 1). Likewise the lesions produced were more severe and extensive than in Group 15.

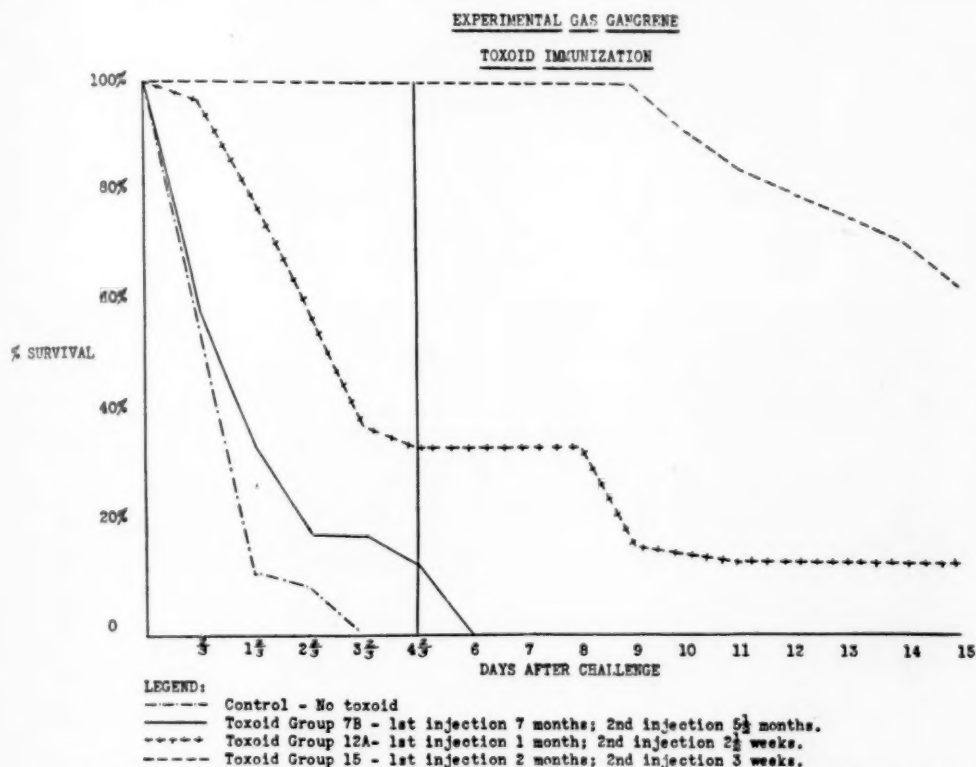


FIG. 1.—Comparing the degree of immunity produced by two injections of *Cl. welchii* toxoid in doses of 30 Lbs. over periods of one, two, and seven months. The results are depicted graphically as the rate and percentage of survival.

An increase in the number of injections to three, using the same dose of toxoid and over a period of two and 2½ months (Group 12B) produced a high degree of protection against challenge, 63 per cent of the animals surviving the 4⅔ day period (Fig. 3). All of the control animals receiving one or more MLDs died in 3⅔ days of fulminating infections.

When the dose was increased to 40 Lbs. and three injections were given at varying intervals (Group 16A, 16B, 16C, and 16D), different degrees of immunity were produced which varied with the time intervals between injection and challenge (Fig. 4). The greatest degree of protection was found in

Group 16A in which the lesions were smaller and less severe and in which 95 per cent of the animals survived the $4\frac{2}{3}$ day period when the injections were made $5\frac{1}{2}$ months, $4\frac{1}{2}$ months, and ten days before challenge.

When each of two doses of toxoid was increased to 60 Lbs. and given at

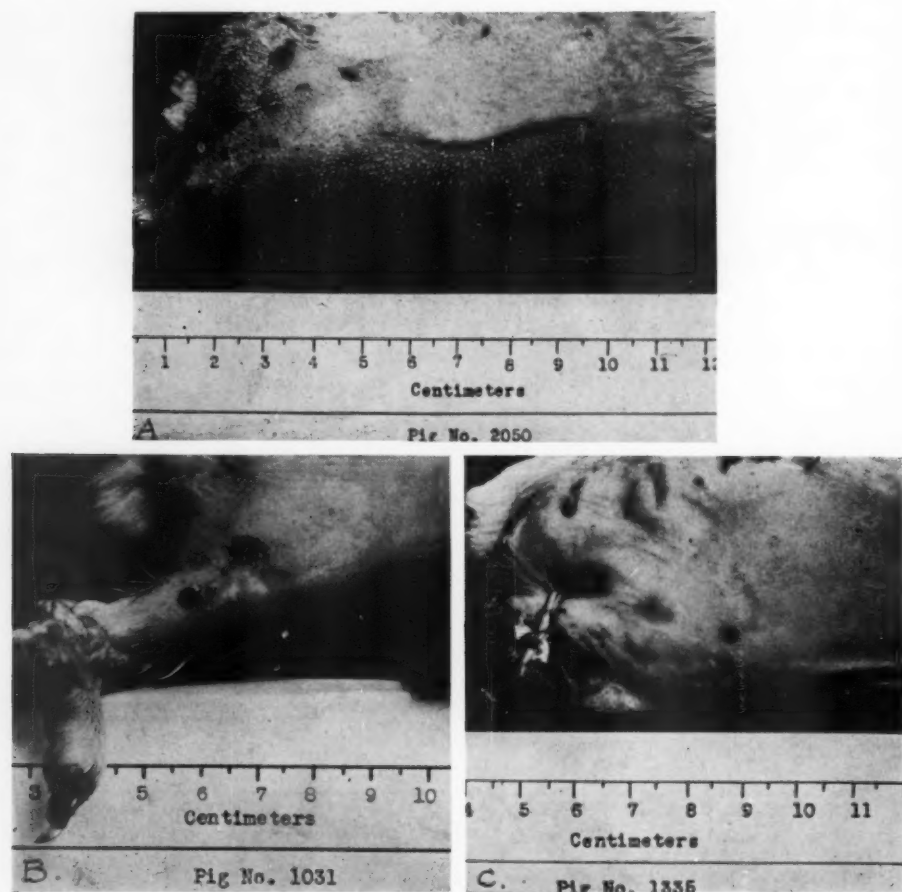


FIG. 2.—Comparing the appearance and extent of the lesions of gas gangrene produced by challenge with 1–10,000 MLDs of *Cl. welchii* culture in representative animals of both control and toxoid immunized groups.

A. An example of the fulminating nature of this infection in an untreated or control animal 24 hours after challenge with 1 MLD of *Cl. welchii* culture. Death occurred 40 hours after challenge. Note extension of process into abdominal and thoracic walls.

B. Showing the very small and healing lesion of clostridial infection in a toxoid immunized animal 16 days after challenge with 100 MLDs.

C. Illustrating the residual lesion of clostridial infection in a toxoid immunized animal that survived challenge with 10,000 MLDs.

one month intervals $3\frac{1}{2}$ to four months before challenge (Groups 17B and 17D), and a third or booster dose of 30 Lbs. was given 10 to 24 days before challenge, from 46 to 65 per cent of the animals survived the experimental infection produced by 1–100 MLDs of *Cl. welchii*. In a third group (17A)

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similarly treated with toxoid but exposed to the overwhelming challenge of 100,000 MLDs only 23 per cent of the animals survived. The highest degree of protection was manifest in that group receiving the first injection $3\frac{1}{2}$ months before challenge (Fig. 5). All of the control animals receiving one or more MLDs were dead within $2\frac{2}{3}$ days of a severe and extensive infection.

Because of the possibility of the toxemia of gas gangrene being produced in part by products arising from degenerating muscle, an attempt was made to measure any additional antigenic effect of injections of trypsin into muscle

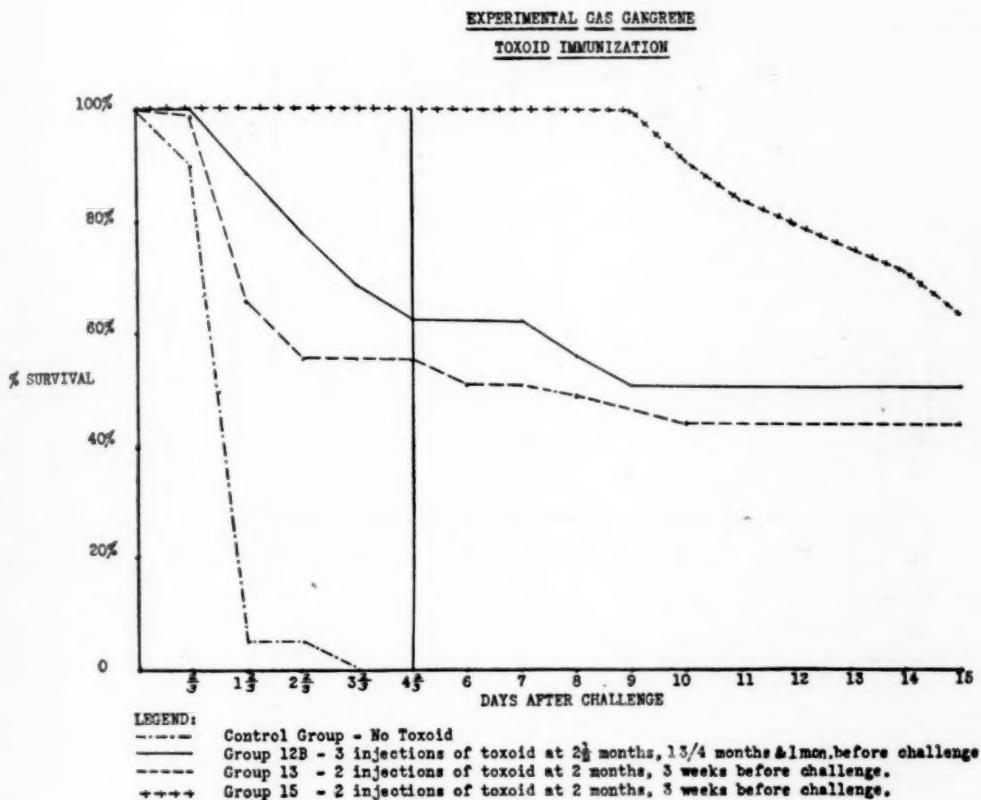


FIG. 3.—Comparing the degree of immunity obtained with three injections of toxoid over $2-2\frac{1}{2}$ month period with that obtained with two injections over the same period using toxoid doses of 30 Lbs.

along with toxoid. A group of 30 animals was subdivided into two groups of 15 animals each (Groups XVIIID and XVIIIDT). Both received three injections of 60, 60, and 30 Lb. of toxoid at four months, three months, and 24 days respectively before challenge. In addition Group 17 DT received 12 daily injections of 8 mgms. of purified trypsin. Challenge with 100 MLD's produced no significant difference in the rate of survival in the two groups (Fig. 6).

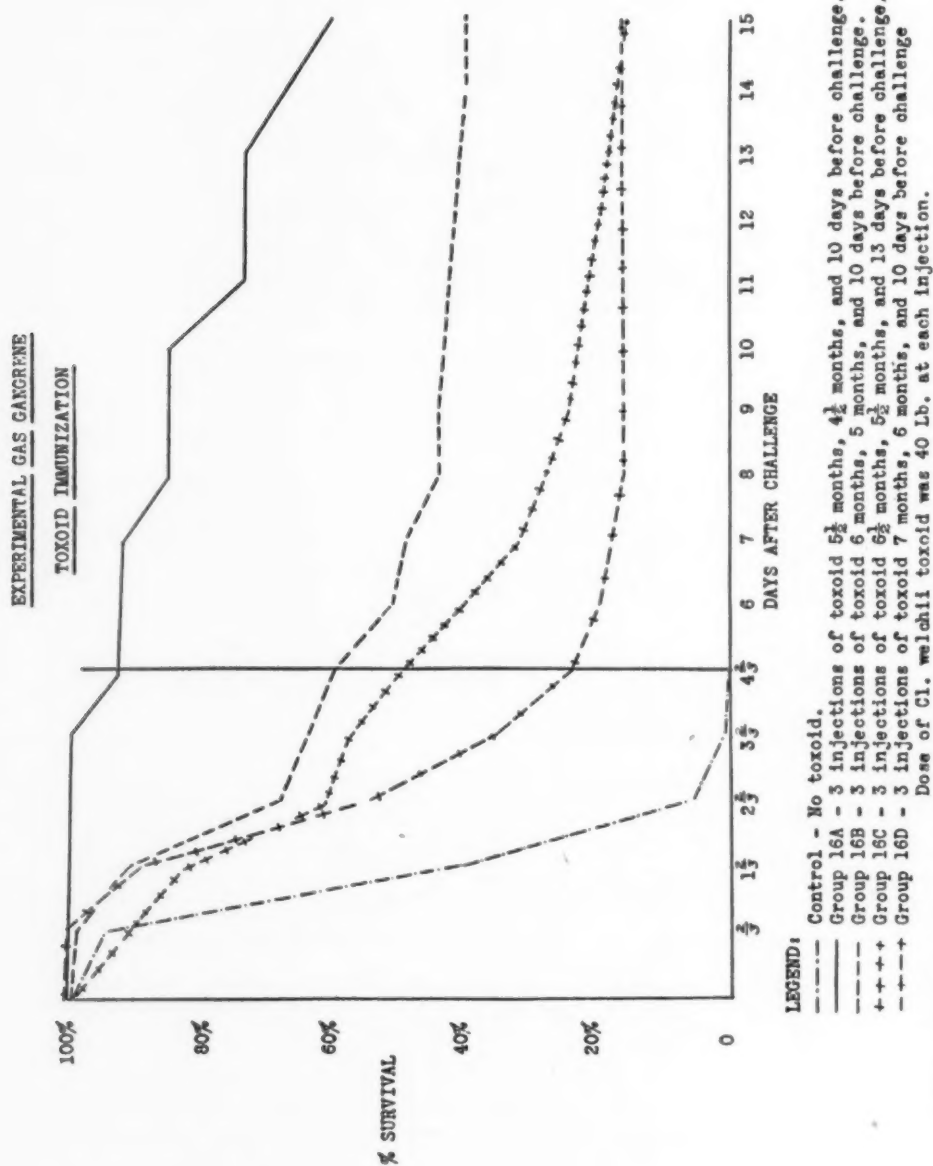


Fig. 4.—Illustrating the diminishing degree of protection produced by three injections of toxoid when the period of immunization was increased from 5½ months to seven months and the third or booster dose was given 10–13 days before challenge.

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Determinations of the serum titers of alpha antitoxin were made in 5-8 representative animals of the different groups. The levels varied considerably, ranging between .05 and 20 units per cc. and averaging two and five units per cc. In Group 15, titers of 10 to 20 units were obtained, and it was in this group that 100 per cent survival of the animals occurred during the test period of 4 $\frac{2}{3}$ days. With this one exception, there seemed to be no correlation between the alpha antitoxin level and the degree of protection in the animals previously treated with toxoid (Table II).

TABLE II

Type of Toxoid	Group	Number of Injections	Antitoxin Level (Units)	Percentage of Survival in 4-2/3 Days
H 21 A	7B	2	1-5	12
H 24	12A	2	.2-10	33
H 24	15	2	10-20	100
H 24	12B	3	.05-10	63
H 24	13	3	.1-5	56
H 24	14A	2	.5-10	70
H 25	16A	3	2-5	95
H 25	16B	3	2-5	60
H 25	16C	3	1-10 (2-5 Av.)	50
H 25	16D	3	1-2	24
H 25	17A	3	2-5	23
H 25	17B	3	1-2	65
H 25	17D	3	2-5	46
H 25	17DT	3	2-5	26
H 25	18A	2	28
H 25	19	2	52

ANALYSIS OF RESULTS

The problem of producing effective immunization with toxoid against gas gangrene is very complex. It is realized that *Cl. welchii* is only one of many causative organisms in this disease, but is the most frequent and probably the most important. Our investigations at this time have therefore been limited to its toxoid so as not to introduce other variables and unknown factors arising from the use of combinations with other toxoids. The problem of effective toxoid prophylaxis against experimental *Cl. welchii* infections alone has been very complicated and difficult. In Table II it will be noted that three preparations of toxoid were used which were made identically in so far as is known from the same basic materials. However, somewhat higher degrees of protection were exhibited by animals injected with toxoid H 24 than those injected with toxoids H 21 A or H 25. In addition the highest alpha antitoxin titers were obtained with toxoid H 24. The significance of this observation has not been determined, but it is known that different preparations of tetanus and diphtheria toxoid show varying degrees of antigenicity. Although the importance of certain factors has not been measured completely, it is evident that a high degree of immunity was produced in markedly susceptible animals against challenge with 1-10,000 MLDs of a highly virulent strain of *Cl. welchii* in the presence of crushed muscle and dirt. According to available informa-

tion, no other type of toxoid has been subjected to such severe tests. In addition it is questionable whether human beings are ever exposed to as many as 1,000 or 10,000 MLDs except under most unusual circumstances.

Early in the investigation, only slight protection was obtained with 12 to 33 per cent of the animals surviving. Subsequently the percentage of survival

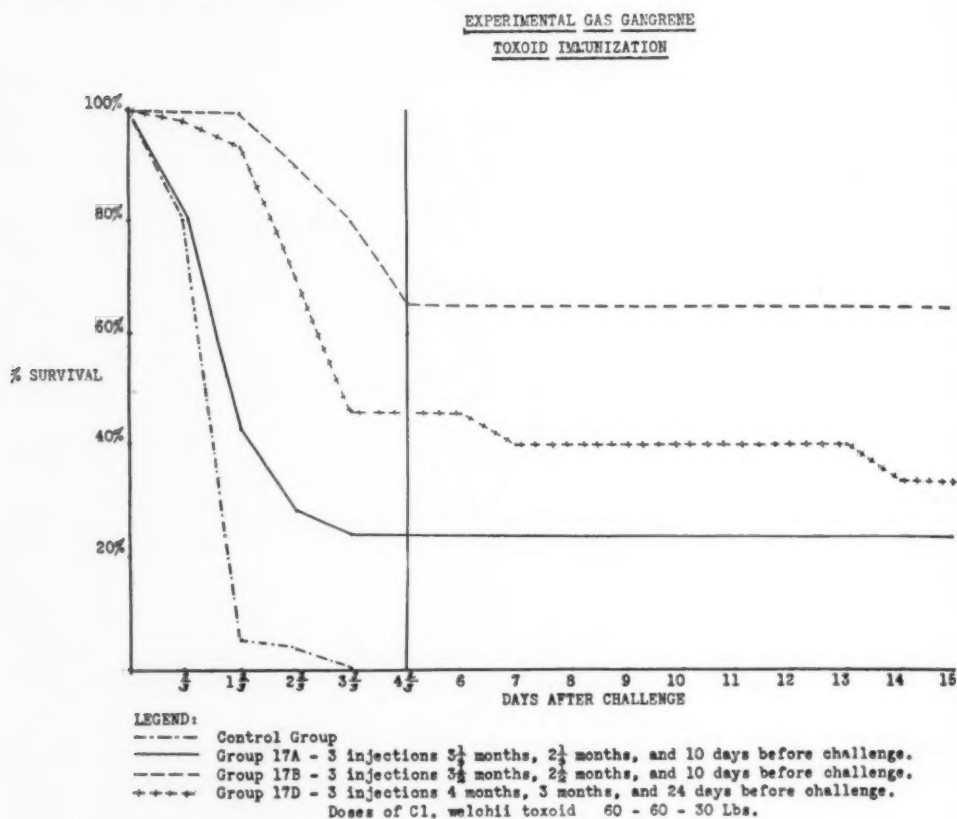


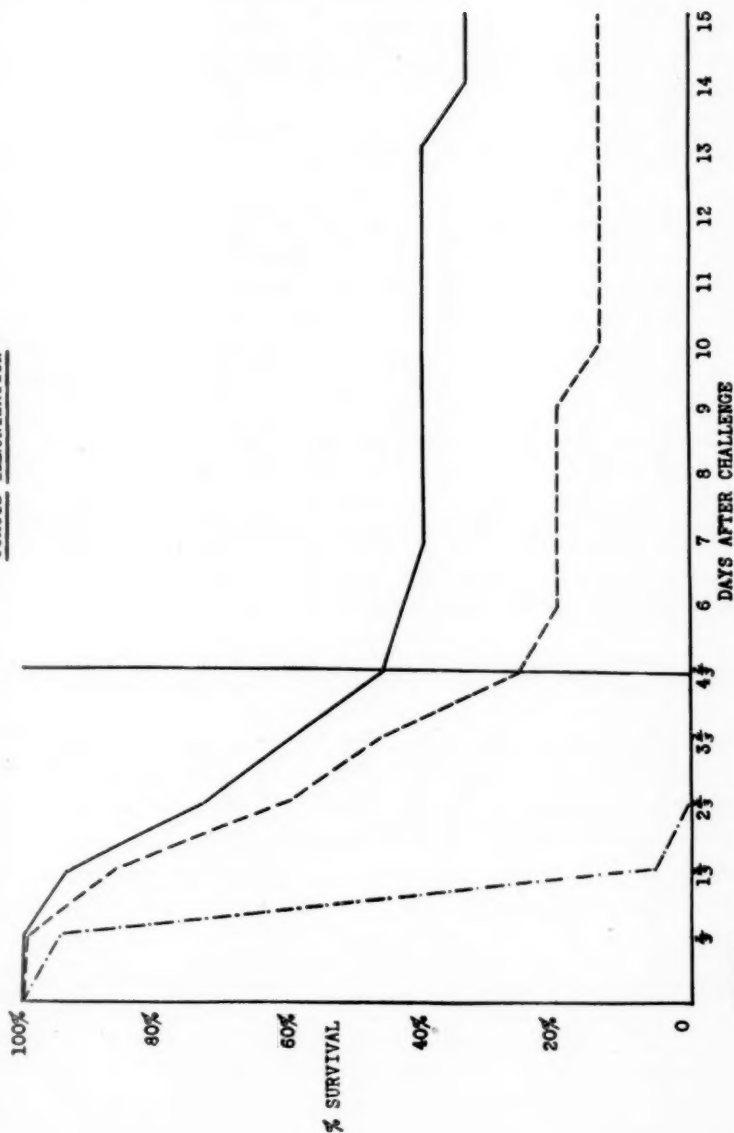
FIG. 5.—Showing the degree of immunity produced by three injections of toxoid during a period of $3\frac{1}{4}$ to 4 months. Group 17A received an overwhelming challenge of 100,000 MLDs.

has been greatly increased, varying between 46 and 100 per cent under different conditions. Because of the limitations of time, the duration and best methods of producing long term immunity have not been established as yet, and further work along this line is imperative.

It is significant to note that serum antitoxin levels of one to ten units of alpha antitoxin have consistently failed to produce adequate protection against this type of infection, and only when the blood titers reached 10 to 20 units was 100 per cent protection obtained. This is contrary to the belief that the presence of 0.1 to 0.25 units per cc. of alpha antitoxin in the circulating blood is the critical level of immunity. Thus the danger of measuring immunity in

EXPERIMENTAL GAS GANGRENE

EXPERIMENTAL GAS GANGRENE TOXOID IMMUNIZATION



LEGEND:
 — Controls
 --- Group 17D Toxoid - 3 injections at 4 months, 3 months, and 24 days before challenge.
 -.- Group 17DT Toxoid - 3 injections of toxoid at same time plus 12 injections with daily dose of 8 mgm. of trypsin.

FIG. 6.—Showing the lack of any additional antigenic effect of trypsin in toxoid treated animals.

gas gangrene on the basis of blood antitoxin levels and the fallacy of assuming that levels of 0.1 unit per cc. will protect human beings from actual infection is emphasized.

In addition, the evidence indicates also that experimental gas gangrene produced in the presence of crushed muscle and dirt is more severe and definitely more refractive to toxoid prophylaxis than the type produced by the simple injection of bacteria, just as it was with chemotherapy.¹⁰ The discrepancy between the high degree of protection (80 to 100 per cent) produced by toxoid injections in animals challenged by the simple injection of toxin or bacteria into healthy muscle and the much lower degree of protection in animals challenged by the injection of bacteria into operative areas containing crushed muscle and dirt suggests the presence of some factor or factors other than the known bacterial exotoxins contributing to the toxemia and mortality of gas gangrene. Our studies suggest that this other toxic factor is produced by the growth of virulent bacteria on the crushed muscle. The presence, nature, and methods of control of such factors are under investigation at the present time.

The production of a high degree of immunity against this severe form of *Cl. welchii* infection in guinea pigs is significant, and it is an indication that effective and complete toxoid prophylaxis is possible in experimental animals, particularly if the nature and control of the other toxic factors can be worked out. Similar experimental studies with toxoids of the other clostridia associated with clinical gas gangrene have been started in anticipation of producing an effective mixed toxoid for ultimate clinical use.

SUMMARY AND CONCLUSIONS

The possibilities of producing effective toxoid immunity against a severe form of experimental gas gangrene developed in the presence of crushed muscle and dirt in animals whose susceptibility and antigenic response are similar to those of the human have been studied. Three hundred and sixty-four guinea pigs injected with *Cl. welchii* toxoid at various intervals were challenged by this method. In the early experiments, the degree of protection was low, being 12 and 33 per cent, although blood antitoxin levels in excess of 0.1 unit per cc. were produced before challenge. When similar groups of animals were challenged with injections of toxin or bacterial culture into healthy muscle, 80 to 100 per cent of the animals were protected by blood levels in excess of 0.1 units per cc.* In subsequent experiments, however, modified procedures of immunization with toxoid have gradually increased the protection to 50 to 100 per cent of animals. The presence of an unknown factor or factors which contributed to the toxemia and mortality of experimental gas gangrene developing in the presence of crushed muscle and dirt is suggested by these studies. The high degree of immunity produced against the severe form of infection indicates that effective immunity is possible by the injection of toxoid against gas gangrene produced by *Cl. welchii*, but the duration of the immunity is undetermined.

Other studies are in progress to increase and extend the degree of immunity afforded by injections of *Cl. welchii* toxoid and to produce similar immunization with toxoids of the other clostridia associated with gas gangrene in anticipation of the development of an effective mixed toxoid for human prophylaxis against clinical gas gangrene.

REFERENCES

- ¹ Jeffrey, J. S., and S. Thomson: Penicillin in Battle Casualties. *Brit. M. J.*, **1**, 4, 1944.
- ² Cutler, E. C., and W. R. Sandusky: Treatment of Clostridial Infections with Penicillin. *Brit. J. Surg.*, **32**, 168, 1945.
- ³ Patterson, T. C., C. Keating, and H. W. Clegg: Experiences in the Prophylaxis and Treatment of Clostridial Infections in Casualties from the Invasion of Europe. *Brit. J. Surg.*, **33**, 74, 1945.
- ⁴ Conway, H.: Anaerobic Infection and Gangrene of War Wounds in Casualties of the Philippine Islands. *Surg.*, **19**, 553, 1946.
- ⁵ Babcock, W. W.: Principles and Practice of Surgery. Philadelphia, Lea and Febiger, 1944.
- ⁶ Caldwell, G. A.: The Prevention and Treatment of Gas Gangrene. Experimental Observations on the Use of the Sulfonamides, Roentgen Ray and Zinc Peroxide. *Tri-State M. J.*, **15**, 2803, 1942.
- ⁷ Carter, B. N., and M. DeBakey: Current Considerations of War Surgery. *ANNALS OF SURGERY*, **121**, 545, 1945.
- ⁸ Kolmer, J. A.: Penicillin Therapy, Including Tyrothricin and Other Antibiotic Therapy. New York, D. Appleton-Century Company, Inc., 1945.
- ⁹ Ogilvie, W. H.: Surgery of Infected Wounds. *Lancet*, **1**, 935, 1940; *Lancet*, **1**, 975, 1940; *Lancet*, **1**, 1019, 1940.
- ¹⁰ Altemeier, W. A., W. L. Furste, W. R. Culbertson: Chemotherapy in Gas Gangrene. An Experimental Study. Submitted for publication in *Surgery*.
- ¹¹ Kolmer, J. A.: Toxoids in Active Immunization Against Gas Gangrene. *J. Immunol.* **43**, 289, March 1942.
- ¹² Stewart, Sarah E.: Antigenic Value of Clostridium Perfringens (Clostridium Welchii) Toxoid in Prevention of Gas Gangrene. *War. Med.*, **2**, 87, 1942.
- ¹³ Robertson, M., and J. Keppie: Active Immunization by Means of Concentrated Toxoid. *Lancet*, **2**, 311, 1943.
- ¹⁴ Dowdy, A. H.: Final Report, August 1, 1943 to January 31, 1945. Summary of Reports Received by the Committee on Medical Research of the O. S. R. D., Bulletin No. 36, page 435, April, 1945.
- ¹⁵ Logan, M. A., A. A. Tytell, and A. G. Tytell: Production of Clostridium Perfringens Alpha Toxin on Peptic Digest of Hog Stomach. Unpublished data.
- ¹⁶ Altemeier, W. A., and W. L. Furste: Studies in Virulence of Clostridium Welchii. Unpublished data.
- ¹⁷ Altemeier, W. A., and W. L. Furste: Gas Gangrene. A Collective Review of the Literature. *Int. Abst. Surg. (Surg., Gyn., and Obst.)*, **84**, 507-523, 1947.
- ¹⁸ Tytell, A. A., M. A. Logan, A. G. Tytell, and Jack Tepper: Immunization of Humans and Animals with Gas Gangrene Toxoids. Submitted for publication in the *Journal of Immunology*.
- ¹⁹ Altemeier, W. A.: The Rapid Identification of the Clostridium Welchii in Accidental Wounds. *Surg., Gyn., and Obst.*, **78**, 411, 1944.

DISCUSSION.—DR. JOHN S. LOCKWOOD, New York: I want to congratulate Doctor Altemeier with warm thanks for this splendid work. The development of a toxoid against *Clostridium welchii* was one of the high priority projects of the Committee on Medical Research during the war. It was the feeling of many of us that the methods of

testing employed by the chemists did not necessarily meet the severe conditions of the types of compound injuries in which gas gangrene so quickly develops. Doctor Altemeier has met this need with brilliant success and has proved that the toxoid against *Clostridium welchii* will meet experimental conditions of great severity. You are all familiar with the success of tetanus toxoid during the last war. It remains to be seen whether a similar measure of success can be achieved with toxoids against the organisms producing gas gangrene. I think we can question whether it will be possible in as short a time to develop as clearcut demonstration of the value of this toxoid as was the case with the toxoid against tetanus. But this large scale clinical experiment will probably have to be carried out some time. I am sure we will all await with interest the later stages of this important and promising study.

MAJOR GENERAL NORMAN T. KIRK, Washington: I want to congratulate Doctor Altemeier on this excellent research work in connection with the protection from gas gangrene diseases by the use of a toxoid. The development of a suitable toxoid for *Cl. welchii* infection had the highest priority so far as my office was concerned during the summer of 1943. A great deal of the work was done in the development of a toxoid by OSRD under the direction of the National Research Council. We were informed that the toxoid had been developed just about the time of V-E Day and that, so far as could be told from experiments with animals, it would give protection. It was our plan to immunize every other division invading Japan with this toxoid to test its worth in the human. Plans were under way to procure this toxoid from civilian sources when V-J Day came.

In World War I there were some 4000 major amputations. I should say that about 50 per cent of these amputations were necessitated to save life from gas gangrene. Fortunately our fears that the incidence of gas gangrene infection would be high in our Army in France did not materialize. There was a minimum of this disease in Italy, particularly in those troops whose evacuation from the site of injury to the forward surgical installations was delayed due to terrain difficulties.

The efficiency of tetanus toxoid was excellently demonstrated in World War II. There were only about eight cases in our Army. It is our hope that an equally effective toxoid can be developed for *Cl. welchii* and other organisms causing this disease before another world conflict. In total war, and with the atomic bomb, the civil population will need this protection as much as or more than the armed forces.

Again my congratulations and appreciation for this excellent bit of work that is being carried out at the University of Cincinnati.

DR. EDWARD D. CHURCHILL, Boston: I wish to emphasize the importance of this investigation not only to the military forces but to the civilian population as well. Doctor Glenn reported last year on the experience with tetanus in Manila. In the Army the incidence of gas gangrene can be reduced greatly by prompt evacuation and proper surgery, but in any disorganized situation, when there is a retreat, when transportation and medical facilities are completely paralyzed, the incidence of gas gangrene goes up immediately. In a disaster that involves the civilian population as war does today, gas gangrene will occur. So this project is one we hope will be continued with first priority.

DR. W. A. ALTEMEIER, Cincinnati (closing): I do not wish to imply that the excision of devitalized tissue in wounds is no longer necessary. This experiment was devised to test to the utmost the immunizing power of gas gangrene toxoid, but for obvious reasons surgical excision of devitalized tissue is just as important as ever. Apparently the antigenicity of preparations of toxoid made at different times has not been uniform, although every step in their manufacture seemed to be identical. Further experimentation is under way to produce toxoids with uniform antigenic activity. Finally, our goal is to develop a mixed toxoid which will be effective for all of the clostridia producing clinical gas gangrene.

I wish to thank all the discussors for their kind remarks.

THE PATHOPHYSIOLOGY OF THE CAUSE OF DEATH FROM CORONARY THROMBOSIS*

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THE EXPLANATION OF THE CAUSE OF DEATH from coronary thrombosis by the cardiologist is frequently ventricular fibrillation or cardiac failure. The explanation of the reason for low blood pressure is very vague. Shock and reflex peripheral collapse are mentioned (Schwartz¹). It seemed to me, that what appears to simulate a picture of shock with low blood pressure, as well as the fibrillation that frequently ensues, are inadequately explained by the theories in vogue at the present time. Measurements of circulation time, rate of blood flow, venous pressure, etc., have all added more information to the subject but have not demonstrated "why" there is a low blood pressure or "why" the heart fails either in fibrillation or without.

It is the purpose of this paper to discuss the results of some experiments that are very incomplete but which show to my mind the following points: (1) Within a few minutes of tying a major branch of the coronary artery there is:

- (a) Blueness over the area of distribution of the vessel.
- (b) Dilatation of this segment of the heart muscle.
- (c) Lack of contraction over this area.
- (d) As soon as contraction of this area ceases there is paradoxical systole of the left ventricle. This probably is the most significant finding in relation to the signs under discussion.
- (e) This is accompanied by an immediate fall in blood pressure
- (f) and a diminished left ventricular output.

If these effects are allowed to continue there is fibrillation and death.

- (2) If the ligature is released from the coronary artery before fibrillation sets in, then all these processes reverse themselves and everything returns to normal.

EXPERIMENTS

(a) The experiments are designed in the following way: With the pericardium open, a suture is placed through the apex of the left ventricle so that the heart is under control. A point on the anterior descending branch of the left coronary artery is selected, proximal to the two or three large terminal branches, over the middle portion of the left ventricle. This leaves one or two branches proximal to the site of ligature. The area of heart muscle supplied by these branches is outlined in one's eye and at roughly the periphery of these areas, two silk sutures are placed through the epicardium as markers, one placed toward the right and the other to the left of the area supplied by these branches (Fig. 1).

* Read before the American Surgical Association, March 26, 1947, Hot Springs, Va.



FIG. 1.—Showing the two markers placed astride large branches of the left anterior descending branch of the coronary artery. A loop of silk is placed loosely and not tied around the artery at the site at which it is to be tied.



FIG. 2.—Shows the similar area after tying the coronary artery. It shows the stretching of the area of the heart demonstrated with an increased distance between the markers. The vessels which are tortuous under ordinary conditions, here are stretched out and are taut.

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(b) Measurements between these markers are made with callipers so that any change in size of this area of the heart can be measured. Next the coronary artery at the site selected above is exposed. The accompanying veins are protected and a silk ligature is placed around the artery at this point.

(c) The artery is tied and the time noted.

(d) Within a few seconds, measurements are continued to be made between the two markers on the surface of the left ventricle.

As well, a large branch of the aortic arch is dissected out, divided and a large bore cannula with a thickwalled rubber tube attached, is inserted and a bull dog clamp applied. The animal is injected with a large quantity of heparin. With this cannula in a large branch, the blood pressure of the aorta is measured on a manometer filled with saline and heparin solution. This rubber tube attached to the manometer is arranged so that it can be disconnected and the output from its end measured in a graduate.

It is noted within a very short time that there is an increasing distance between these two markers, indicating an expansion of the area of heart muscle supplied by the vessels which are now occluded (Fig. 2).

(e) Within one to one and a half minutes, the maximum expansion of this area of heart muscle is obtained and in all cases the expansion has been about 25 per cent above the measurements found, before the coronary artery was tied.

Before and after the ligature is tied on the coronary artery, the blood pressure is taken continuously on the manometer and the results have shown invariably that there has been a fall in blood pressure (Table I). This begins

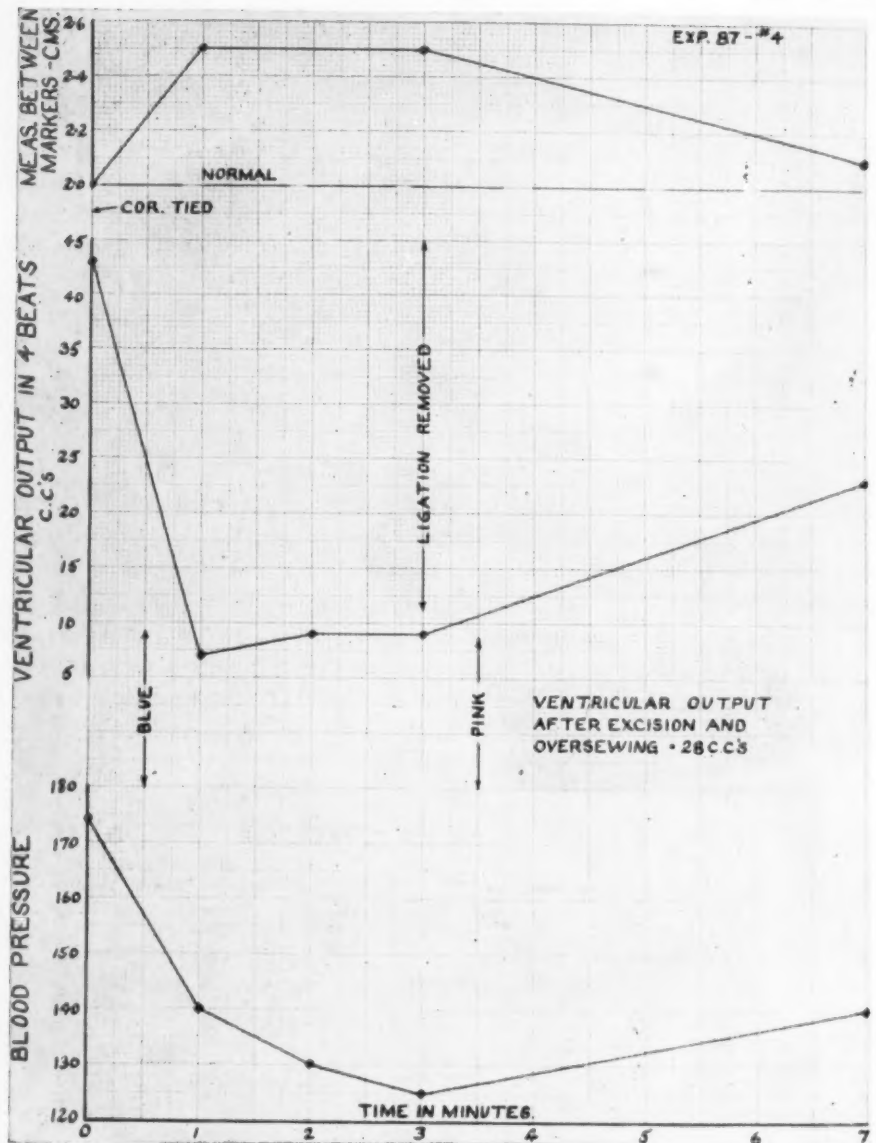
TABLE I
SHOWING THE TIME IN SECONDS FOR THE MAXIMAL INCREASE OF DISTANCE BETWEEN THE MARKERS

Exp. No.	Maximum Increase Between Markers		Time in Seconds	Exp. No.	Maximum Increase Between Markers		Time in Seconds
	Cms.				Cms.		
H1	0.5		60	H4	0.5		150
H2	0.65		120	H5	0.7		150
H3	0.6		180	H6	1.0		180

not immediately on tying the coronary artery, but becomes evident when there is obvious lack of contraction with stretching and dilatation of the area of the heart, which is about to become the infarct.

It is arranged at this stage that the cannula in the aortic branch is disconnected from the manometer, during some of the experiments, so that the output of the heart can be measured before and after (Graph I). This is done by allowing an open flow of blood through the large-lumen tube, directly into a graduate. The amount of output of the heart has fallen very considerably on all occasions (Graph II).

The cardiac output experiment is done frequently with the aorta unclamped and in other cases it is done with the aorta clamped off distal to the branch being used, so that most of the ventricular output appears through the open cannula. After withdrawing the blood, which is measured for five beats

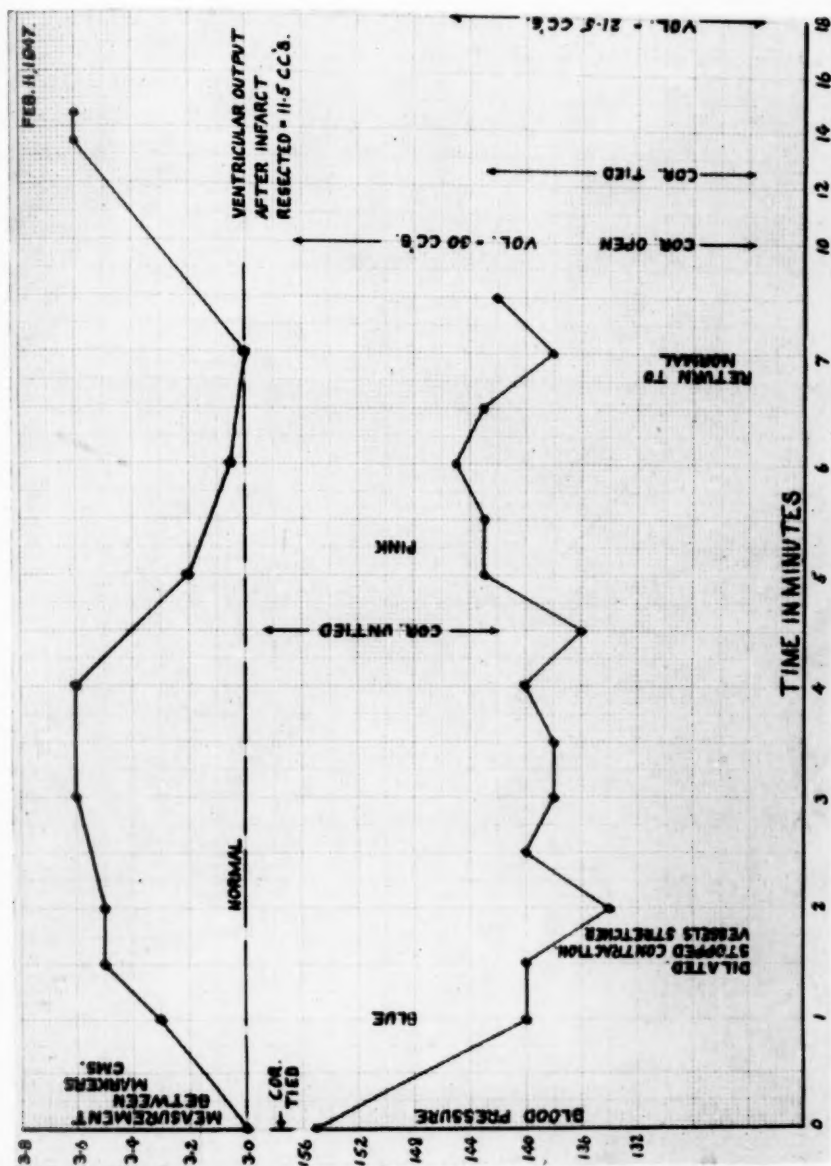


GRAPH I.—Graph showing the effect produced following ligation of the coronary artery. There is:

- (1) An increased distance between the markers as shown in the measurements in the upper line.
- (2) The next line shows the blood pressure fall.

When the tie is removed from the coronary artery within two to three minutes the infarcted area regains its color. Its expansion shrinks down to normal again. The vessels again become tortuous. The blood pressure and cardiac output return to normal and the distance between the markers returns to normal. If, however, the tie is left on too long, the condition becomes irreversible. Then the infarct remains as a permanent effect and within a very few minutes the animal will die. With an infarct which does not recover, the animal is losing his blood pressure and cardiac output, there is visible dilatation of the right heart until this becomes enormous. In other words, the left ventricle is unable to put out the amount of blood which is returned to it and this goes through a progressive change until with failure of the left ventricle, the right ventricle is dilated enormously and ultimately fails with fibrillation of both left and right ventricles.

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GRAPH II.—Showing increased distance between markers and fall in blood pressure with diminished output with coronary tied, then untied and finally tied again.

on each occasion, the blood is returned to the animal so that the blood volume is not changed throughout the remainder of the experiment.

Electrocardiographic tracings are also made during the different stages of doing this experiment so that the effect here can be compared with those which can be demonstrated by the other methods of investigation.

To prevent the expansion of the infarcted area a patch of firm cloth is stitched to the epicardium around the periphery of the area to become infarcted, before the artery is tied off. This is stitched down in such a way that the cloth is taut and will tend to prevent bulging when the infarct begins to make its appearance. Under these conditions there is a drop, but less of a drop of blood pressure and not so great a fall in the cardiac output.

RESECTION OF VENTRICLE

The next part of the experiment has to do with an attempt at overcoming the effect of such a coronary occlusion. When the artery has been tied off and



FIG. 3.—Shows the infarct resected and still holding by a pedicle which will be removed. The sutures are in place.

there is maximal dilatation of the area to be infarcted, with the fall in blood pressure, and the diminished cardiac output, then an attempt is made to resect the infarcted area of the left ventricle (Fig. 3). This has been accomplished quite satisfactorily in 25 dogs and has been done in the following way:

The area infarcted is easily visible. A continuous mattress type of cat-gut suture is passed through the ventricle approximating the margins of the infarcted area leaving the infarcted area projecting out of the cardiac cavity as a loop. When this has been tightened up, fairly satisfactory hemostasis is obtained. The infarcted area can then be excised quite neatly with a scalpel, taking care not to cut the suture which is vital at this time. Following re-

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moval of the infarct, the area is again oversewn and a satisfactory repair can be obtained. In some, the total repair has been done with cat gut, in others silk sutures have been applied on the surface to add more support.

The results of removing this infarct produce an astonishing effect in the animal. The cardiac output increases considerably and the blood pressure rises moderately, although it does not return to the original level. When this has been done satisfactorily, the animal which one would judge, from control experiments, would die, survives quite satisfactorily and most of them have made quite a good recovery. In my experience, I would think that practically all animals in whom we had resected this area, would have died of dilatation and finally fibrillation and heart failure. It is interesting, therefore, that many of these animals are alive and quite well for as long as one to two years later.

The accompanying photographs show the cross sections of hearts of animals which were sacrificed at the times given and show the state of the wall of the ventricle after resection of the infarct (Figs. 5, 6 and 7) at the various intervals. These animals following resection of the ventricle are not in bad health but recover very quickly and within a short time carry on as do normal animals. There seems to be no limitation of function and no disability on this account. They are quite vigorous and strong and have plenty of energy.

DISCUSSION

My thoughts and experiments on this subject lead me to believe that when a coronary attack occurs, whether it be spasm or complete occlusion, an infarct is produced in the heart muscle. If it is placed so that it involves the conducting mechanism, it may interfere with conduction and embarrass the heart, from that point of view. If the conducting mechanism is not involved, then it produces an area, which within a very short time is non-contractile. This area becomes dilated and acts as an expansion chamber. When the ventricle contracts, varying amounts of the blood of the ventricle, depending on the size of the infarct, are forced into this elastic chamber. The effectiveness of the contraction is partly lost because of this expanding chamber and consequently the amount of blood delivered into the aorta is much diminished. This paradoxical systole (Fig. 8), to my mind, probably accounts for many of the symptoms from which the coronary patient suffers, namely low blood pressure, signs of shock, lack of energy, and all the symptoms related to this lack of adequate peripheral circulation. It provides an explanation for the picture of shock which is evident in many of these patients. If the condition persists or the infarct is of a fairly large size, depending on the reserve power of the remainder of the heart, the patient goes through progressive changes until ultimately fibrillation or failure occurs, but these are terminal events only.

The medical treatment of such a condition can be palliative only. Measures to try to increase the blood pressure and blood volume may improve the situation somewhat, but there is nothing that can be done to this expansion chamber, produced by the infarcted area, to make it function better. There

are no drugs that have any effect on this. They may whip up the remaining heart muscles to make a greater effort, but much of this effort is lost in the expansion chamber. This is a situation somewhat similar to the state of affairs in an arteriovenous aneurysm or peripheral aneurysm elsewhere. In a clinical patient it is possible that the degree of fall of blood pressure, is a measure of the size and significance of the expansion chamber, produced by the infarcted area. This is fairly well born out by the fact, that clinicians are quite aware, that the patient who has a very low blood pressure, is the patient who is in the more critical condition, as a result of his coronary occlusion.

TREATMENT

While it is obviously facetious at this stage to make the following remarks, still I have a conviction that, as medical treatment is so ineffective, and is entirely helpless, except from a palliative point of view, the day may come, when the best plan of dealing with a coronary thrombosis, would be an emergency operation. This should be undertaken before the patient gets a large expansion chamber, which will ultimately cause heart failure. The approach is not difficult, and the right or left coronary areas could easily be excised and repaired with relative safety. This would accomplish two things: (1) It would overcome the immediate effect of the expansion chamber and save the patient from cardiac collapse. (2) As well it would remove the infarcted area, so that the coronary artery, which was occluded, would from then on, be of no significance. It would as well, remove the part of the heart in which a cardiac aneurysm may develop and which ultimately may rupture. As well it would relieve the patient of the dangers of acute rupture of an infarct, within a few days of the time of infarction.

This perspective, then places on the cardiologist the responsibility of being able to decide, just where in the heart, is this infarcted area. If it involves the anterior descending branch of the left coronary, which is the commonest site, this is readily accessible, and is quite easily dealt with surgically. If it involves the posterior surface of the left ventricle, or the left lateral surface, this also is easily dealt with. The area so far, which is relatively inaccessible, is the septal area but with an infarct involving the septum, if it does not interfere with the conducting mechanism, it is supported somewhat, by pressure of the right ventricle, and so far as I can see from recorded writings,² is less likely to produce aneurysms, ruptures and the other acute catastrophies.

As this is making drastic inroads on the physician's territory, I have some doubts if my colleagues in medicine, will consider, that surgical treatment of this lesion is reasonable. Possibly I may not see a suitable case on which this could be done, but I feel at the present time, that in a properly selected case, this could be done with dispatch, with less danger than waiting for the unpredictable effects of the coronary occlusion to develop, and that ultimately the patient might be cured.

The question of the anesthetic is not a serious one, because there is some evidence to suggest that a patient under ether anesthesia is in less danger

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FIG. 4.—Shows the infarcted area removed and the defect repaired by sutures giving satisfactory hemastasis.



FIG. 5.—Photograph of a cross section of the left and right ventricles showing the site of resection of an infarct one year previously. There is scar uniting the muscle on each side. There is a good lumen to the left ventricle and the remaining muscle is normal.



FIG. 6.—Low power of scar at site of resection of infarct of left ventricle.



FIG. 7.—Photomicrograph showing the appearance of the scar uniting the left ventricle at the site at which the infarct was excised.

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with a coronary occlusion, than he is without the anesthetic. It might be a valuable measure to apply, for its immediate effect, and if the infarcted area were resected, the patient might waken up with better prospects of survival, and of cure of his disease, from this particular attack.

SUMMARY

(1) A condition of paradoxical systole has been demonstrated experimentally in hearts in animals following coronary occlusion.

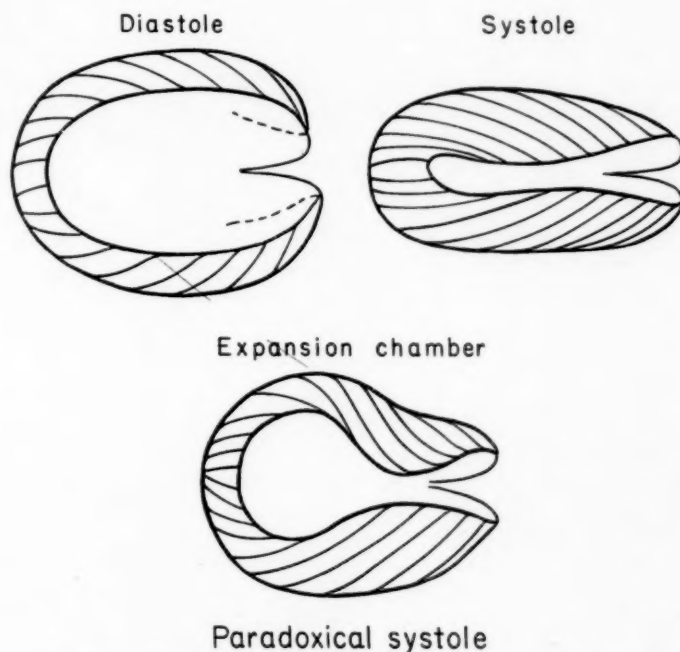


FIG. 8.—Diagrammatic representation of a ventricle in full dilatation; then the relative occlusion of the cavity with systole, and next the diagrammatic representation of the expansion chamber produced by the infarcted area which makes it impossible for the ventricle to empty itself or to deliver its regulation amount of blood, both because of the expansion chamber and secondly because there is less muscle area in its wall with the ability of contraction to expel the normal contents.

(2) This state is accompanied by a fall in blood pressure and diminished cardiac output.

(3) Following resection of the infarcted area in the heart, there is an improvement in blood pressure and in cardiac output.

(4) It has been demonstrated that compared with a control group of animals, the prospects of survival are 80%.

(5) It was suggested that the best treatment of acute coronary occlusion in the human being in selected cases might be, by immediate surgical operation. This would provide:

- (a) A better chance of survival from the effects of a severe and large infarct from a major occlusion and
- (b) A cure of the patient from an infarcted area of the heart which would eliminate the dangers of acute rupture, aneurysm and subsequent rupture. It would remove all the effects of a coronary occlusion.

REFERENCE

- ¹ Schwartz, Wm. B.: The Treatment of Shock Accompanying Myocardial Infarction. *Am. Heart J.*, **2**, 169, 1947.
- ² Harrison, R. T.: Failure of the Circulation. Baltimore, Williams and Wilkins Co., 1939.

I acknowledge with pleasure the technical assistance of Mr. Newell Thomas and Dr. E. Delorme employed by the author, and Dr. Ray Heimbecker for his photography. This work was done without University or other assistance, apart from limited laboratory facilities in the Banting Institute.

DISCUSSION.—DR. ALFRED BLALOCK, Baltimore: I was sitting next to Dr. Rudolph Matas while Dr. Gordon Murray was presenting his paper and he stated to me that this work may be epoch-making. The lack of prolonged discussion is probably due to the fact that others are as amazed by these brilliant experimental observations as I am.

There is no more important problem in medicine and surgery than that which Doctor Murray is tackling. Coronary occlusion ranks high in the list of causes of death. A great deal of work is being done in various laboratories in an effort to find a satisfactory treatment for this common disorder. Fortunately more money will be available in the future for additional studies on heart disease.

It is only natural that Doctor Murray would hesitate to transfer immediately his experimental observations to the treatment of the patient. When one realizes that the average survival period of patients who survive the first attack of coronary occlusion is approximately five years, one hesitates to carry out what appears to be at this time a radical surgical procedure. I doubt if such a procedure appears to us to be more radical and bold than did the suture of heart wounds 50 years ago.

The fact that Doctor Murray was able to prevent the death of animals following coronary occlusion by excision of the infarcted area is a magnificent accomplishment. I believe that there will ultimately be a clinical application for his findings and it is to be hoped that Doctor Murray will continue and extend his studies.

FACTORS LIMITING SURGERY FOR ESSENTIAL HYPERTENSION*

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INTRODUCTION

THE SURGICAL TREATMENT of essential hypertension has been based on the concept that it is due to overaction of the sympathetic nervous system. Such overactivity has been attributed either to a disturbance in the higher functions of the brain, or to a decrease in the inhibitory influence of the moderator afferent nerves from the carotid sinus and the arch of the aorta. The increased activity of the sympathetic nervous system has been pictured as causing general or local vasoconstriction and an increased secretion of epinephrine. More recently such overaction has been regarded as responsible for the constriction of the renal blood vessels, thus leading to a release of renin.

To counteract the effect of sympathetic overaction and to lower the blood pressure, it has been deemed advisable to enlarge the vascular bed by denervation. In addition, the operations also denervated the adrenal medulla and the kidney blood vessels.

It is the purpose of this paper to present evidence that the entire concept of overactivity of the sympathetic nervous system as an important and primary cause of essential hypertension should be abandoned. It is also hoped that the presentation of a new concept of the pathogenesis of essential hypertension will indicate how operations on the sympathetic nervous system can modify the initiating factors of essential hypertension. Knowing these facts, it will be possible to outline the limits beyond which some operations as now practised are useless and may be harmful.

EFFECTS OF OVERACTION OF SYMPATHETIC NERVOUS SYSTEM

Through experimental and clinical observation the manifestations of overaction of the sympathetic system are well known. Among those easily recognized are dilation of the pupil, pallor of the skin, increased activity of the sweat glands, tachycardia, salivation, hypertension of the diastolic type and hyperglycemia. Restlessness and tremor are characteristically present, an indirect effect of epinephrine release. Similar signs and symptoms are exhibited in persons in whom tumors of the adrenal medulla cause diastolic hypertension. It is accepted that the excess release of epinephrine has effects similar to overaction of the adrenergic fibers of the sympathetic nervous

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system. However, in persons with essential hypertension such evidence of overaction of the sympathetic nervous system is not seen. They are exhibited to a marked degree in children with acrodynia, where diastolic hypertension is a constant finding.

THE CIRCULATION IN ESSENTIAL HYPERTENSION

Studies of the circulation in essential hypertension have shown that the raised arterial pressure is not due to an increased cardiac output or to increased blood viscosity, for these have been measured and found normal. It is recognized that diastolic hypertension is due to narrowing of the small arteries and arterioles. The hydrostatic pressure within the capillaries, the venules and the veins is normal. Intensive studies of the conditions of blood flow through the various tissues of the body such as the skin, the muscles, the brain and the kidneys in essential hypertension have been carried out (Pickering, 1935). It has been found, for instance, that the arterioles of the skin are narrowed, but that when the vasomotor influences are removed reflexly or by chemical block, the increase in blood flow is no greater, but sometimes a little less in subjects with benign and malignant hypertension than it is in subjects of comparable age with normal pressures. On such evidence it has been concluded that in essential hypertension the hand vessels are narrowed by a non-nervous agent, and this narrowing is of an order which, if generally distributed throughout the body, would account for the hypertension. Since the skin vessels are rarely and inconsiderably involved in the arteriosclerosis of hypertension, the narrowing is presumably not of structural but of humoral origin. Goldring, Chassis, Ranges and Smith (1941) have investigated, through the use of diodrast and inulin clearances, the renal circulation in 60 cases of essential hypertension of all grades of severity, and found that the effective renal blood flow as inferred from the diodrast clearances was reduced, the rate of the glomerular filtration is much less reduced than the tubular function so that the fraction of the renal blood flow filtered off into the glomeruli is increased. They also found that in all but three cases the renal excretory mass was reduced. It was evident from their studies that in hypertension, including essential hypertension, the efferent glomerular arteries are constricted. These investigators concluded likewise that in essential hypertension the vasoconstriction in the renal arterioles is not nervous in origin because the renal blood flow is not increased, nor is the filtration fraction lowered by operations in which the sympathetic nerve supply to the kidneys has been divided.

The second hypothesis, that essential hypertension could result from overaction of the sympathetic nervous system because of underaction of inhibitory influences normally arising in the carotid sinus and the aortic arch, received support when it was shown by Koch, Mies and Nordmann (1927) among others that section of the carotid sinus and the depressor nerves could produce hypertension. However, it was shown by Pickering, Kissin, and Rothchild (1936) that the carotid sinus mechanism is active in essential hypertension

and the tachycardia, which is a constant feature of this type of experimental hypertension, is not present in humans with essential hypertension.

Evidence that in essential hypertension the vascular narrowing is humoral and not primarily nervous, is found also in the observation that during surgical anesthesia with ether when the skin is pink, indicating vasodilation, the blood pressure remains well elevated above the levels observed in persons with normal blood pressure under similar conditions. The persistent elevation of the blood pressure cannot be attributed always to generalized occlusive changes because the blood vessels as seen in muscle and renal biopsy material may show minimal degrees of occlusive narrowing (Castleman and Smithwick, 1943).

THE PATHOGENESIS OF DIASTOLIC HYPERTENSION

The results of studies of Cushing's syndrome have been utilized as a basis for a concept of the pathogenesis of essential hypertension because in both states there invariably develops diastolic hypertension and arteriolar sclerosis. Studies of the circulation in Cushing's syndrome have demonstrated that it is similar in its essential characteristics to that exhibited by persons with essential hypertension. Thus, the skin vessels in each are constricted but the degree of constriction is such that the blood flow through them under the existing increased arterial pressure is normal or only slightly reduced. In both the efferent glomerular arterioles are constricted first, and then with progression of the disease processes the total renal blood flow also is reduced.

The primary causes of Cushing's syndrome have been shown to be a tumor of the adrenal cortex, a tumor of the thymus, a tumor of the ovary, or an atrophy of the hypothalamic nuclei, particularly the paraventricular and the supraoptic (Heinbecker, 1946). These are the nuclei which innervate the neural hypophysis and control its function. It has been established that most, if not all, persons with Cushing's syndrome, regardless of the primary cause, exhibit some degree of polyuria and of polyphagia. It has also been established that regardless of the primary cause, there occurs a degeneration or hyalinization of the basophil cells, while the eosinophil cells are relatively or actually increased in number. Evidence of overaction of these eosinophil cells is indicated by a decreased insulin sensitivity, by a decrease in the lymphocytes of the circulating blood, by masculinization, and by the development of obesity. Evidence for these statements is based on the results of experimental studies previously reported on (Heinbecker, 1944), or now in process in our laboratory. For dogs, it has been concluded that the eosinophil cells are trophic to the adrenal cortex. This harmonizes with the observation of functional overaction or of hypertrophy so frequently encountered in persons with Cushing's syndrome when no actual tumor of the adrenal cortex is present. The hyalinization or degranulation of the basophil cells is considered to be associated with underaction, because of the elevated blood cholesterol and the diminution in basal metabolic rate observed in such persons. Experimentally it has been shown that the basophil cells are trophic to the thyroid gland and to the germ cells.

An experimental basis for the preponderance of the eosinophil cells with a depression of the basophil cells has been obtained in experimental studies in the dog (Heinbecker, White and Rolf, 1944). It has been established that when the neural hypophysis is denervated a marked cytological change occurs in the glandular hypophysis. Basophil cells disappear, while the eosinophil cells are preponderant and apparently overactive. The interpretation is made that through loss of the secretion of the neural hypophysis, or its neutralization when a tumor of the adrenal is the primary cause, maturation of the basophil cells fails to occur, while the eosinophil cells mature and are stimulated. A similar but less marked preponderance and overaction of the eosinophil cells follows a lesion in the posterior hypothalamus severing the fibers between the thalamus and subthalamus and the paired paraventricular nucleus. It also follows a production of partial asphyxia of one adrenal and the wrapping of one kidney in silk with removal of the other. It is significant that these experimental procedures give rise to varying degrees of diastolic hypertension. There develops in pregnancy also a preponderance of eosinophil cells in the glandular hypophysis. It is presumably due to overaction of these cells that there develops an enlargement of the adrenal glands. In those constitutionally susceptible, pregnancy may be associated with the development of diastolic hypertension.

Evidence from experiments on dogs, which will be presented in detail elsewhere, is believed to afford an explanation of the manner of development of diastolic hypertension in these various states. It has been found that following the administration of an extract from the anterior lobe of the pituitary or of adrenal cortical extract or, and particularly, by the simultaneous administration of these two extracts there results a constriction of the efferent glomerular arteries (Heinbecker, Rolf and White, 1943; White, Heinbecker and Rolf, 1947, in press). This in turn, by decreasing the blood flow to the renal tubules, is considered to lead to a release of renin. The combined action of these three humors is held responsible for the extra-renal arteriolar narrowing and thus for the development of diastolic hypertension.

To account for the development of hypertension in persons where there are no recognizable primary causes such as have been demonstrated in Cushing's syndrome, and who therefore have been designated as having essential hypertension, it is postulated that functional influences in the central nervous system, particularly in the frontal lobes of the cerebral cortex, normally may depress the hypothalamic nuclei which control the secretion of the neural hypophysis. The anatomic and physiologic bases for such influences are well established. On depression of the functional activity of these nuclei there results a diminution in the secretion of the neural hypophysis. This, on the basis of the experimental evidence presented, can be assumed to result in a stimulation of the eosinophil cells of the glandular hypophysis and these in turn to stimulate the adrenal cortex to greater activity. The combined influence of the anterior pituitary hormone and of the adrenal cortical hormone is to effect a constriction of the efferent glomerular arterioles of the kidney and

a release of renin. The combined action of all three humors here as in Cushing's syndrome is held responsible for the arteriolar narrowing and the development of diastolic hypertension.

It is apparent that according to this hypothesis all persons with diabetes insipidus might be expected to develop essential hypertension. Analysis of recent cases at Barnes Hospital has revealed that four of 12 persons with persistent marked diabetes insipidus, indicating thereby the presence of some glandular hypophysis (Heinbecker, White and Rolf, 1947) exhibited a diastolic blood pressure above 100 mm. Hg. While this percentage incidence is higher than that which occurs in the normal population it indicates nevertheless that in order to account for the development of essential hypertension in persons who do not exhibit diabetes insipidus, it is necessary to postulate that not only must there result a sufficient functional depression of the neural hypophysis as a result of influences within the nervous system, particularly from the frontal cortex, but there must be also a susceptibility of the smooth muscle of the blood vessels to the vasoconstricting action of the humoral agents involved in the production of diastolic hypertension.

Other experimental evidence indicates that the combined overaction of the eosinophil cells and the adrenal cortical hormone increases the deposition of neutral fats in certain tissues, including the blood vessels, and raises the cholesterol content of the plasma (Heinbecker, White and Rolf, 1944, loc. cit.). Evidence indicating that such metabolic disturbances are of primary importance in the development of arteriolar sclerosis in persons with Cushing's syndrome has been presented (Heinbecker, 1944, loc. cit.). It seems reasonable to assume that they play a similar role in the development of the arteriolar sclerosis when associated with essential hypertension. Thus, the same influences which lead to hypertension are regarded as leading to the arteriolar changes associated with it.

DISCUSSION

If one accepts the implications of the studies of the circulation in diastolic hypertension, it is clear that such hypertension can no longer be attributed mainly to overaction of the vasomotor nervous system. Likewise, an analysis of the clinical signs and symptoms exhibited by persons with essential hypertension lends no support to the idea. In contrast, the clinical signs and symptoms associated with the diastolic hypertension in persons with acrodynia and in the hypertension associated with epinephrine secreting tumors, the pheochromocytomata, are easily recognizable and in clear agreement with the responses of stimulation of sympathetic nerve trunks or of the intravenous injection of epinephrine in man and the experimental animal.

The concept of the pathogenesis of diastolic hypertension herein presented affords an explanation for many difficulties associated with the acceptance of others previously presented. First, it offers a reasonable explanation as to how functional disturbances in the central nervous system can modify the function of the glandular hypophysis and thereby of all endocrine glands

normally under its trophic influence without the existence of any direct nervous connection between the neural and the glandular hypophysis. It also provides a mechanism for the constriction of the efferent glomerular arterioles of the kidney, and thereby for the release of renin other than overaction of the sympathetic nervous system. Clinical studies of hypertension have shown that the latter hypothesis is not tenable. The concept presented here provides for an initiating humoral mechanism for the activation of a renin mechanism not of primary origin in the kidney. The fact that constitutional susceptibility must be assumed to explain the development of hypertension by this mechanism is regrettable from the physiological standpoint, but is in accord with well supported clinical observations. It is consistent with the evidence that with depression of the secretion of the neural hypophysis there occurs a sensitization of the smooth musculature, including that of the blood vessels to epinephrine (Heinbecker, 1937) to adrenal cortical hormone and to renin (Heinbecker, unpublished data).

The implications of the concept of the pathogenesis of hypertension pertinent to our problem are that there are but two organs producing the hormones concerned in the causation of essential hypertension which can be modified by sympathectomy. These are the kidney and the adrenal gland. The results of anatomic investigations concerning the innervation of the kidney and the adrenal glands are in agreement in showing that the nerves to the adrenal gland and the kidney pass from the celiac ganglion and the upper two lumbar ganglia. The fibers which go to the celiac ganglion are derived from the three splanchnic nerves. Any operation which sections the splanchnic nerves prior to their junction with the celiac ganglion and the upper two lumbar ganglia must therefore effectively denervate the adrenal gland and the kidney.

The effect of a removal of sympathetic nerves more extensive than that outlined above can be only to temporarily enlarge the vascular bed under such sympathetic control. That the enlargement is temporary has been well established by the experimental work of Cannon (1932) and of others. After a period of time has elapsed, the arteries return to their normal calibre through the action of an intrinsic mechanism which is not nervous in character. Reflex narrowing of the denervated vessels is eliminated. This, however, for reasons stated is not deemed significant in the pathogenesis of essential hypertension.

The adrenal cortex is not directly innervated by the sympathetic nervous system. The adrenal medulla, on the other hand, is dependent upon sympathetic innervation for its secretory activity. Denervation of the adrenal medulla is regarded as of great significance in the treatment of essential hypertension. A decrease in the amount of its secretion is held to be responsible for the depression of the excitability of the central nervous system for influences which normally lead to a depression of the hypothalamus. The evidence in support of this concept is both experimental and clinical. Electroencephalographic studies in the cat, carried out in our laboratory, have shown that epinephrine has a profound excitatory influence on the activity of the central nervous system including the frontal lobe. The increased activity is demon-

strated by an increase in amplitude and frequency of the waves recorded from the surface of the brain (Heinbecker and Bartley, unpublished data). The effect of epinephrine on the isolated, spontaneously active ganglion cells on the limulus heart cord is to increase the frequency and the magnitude of the ganglion cell response (Heinbecker, 1933). The assumption is therefore made that a marked decrease in circulating epinephrine would lead to lessened irritability of the cells of the central nervous system, particularly those of the cerebral cortex.

It must be admitted that hypertension may serve a useful purpose. Even with the elevation in pressure the circulation to the various tissues of the body is not increased. It is known that the flow to the kidneys may be decreased. Only in the kidneys does there exist an intrinsic mechanism for increasing the blood pressure and thereby the renal blood flow. Present evidence indicates that renin is released whenever the circulation to the renal tubules is decreased. In extensive sympathectomy the temporary increase in the size of the vascular bed results frequently in a decrease in blood pressure without any increase in blood volume. There is evidence that the cardiac output is decreased (Grimson, 1946). Because of these facts it follows that if the vascular narrowing in the kidneys is primarily humoral and non-nervous, the shunting of blood from the kidneys which must result from extensive sympathectomy would not only impair the renal function but also increase the release of renin which may be markedly injurious to the blood vessels of the body if sufficient in amount.

The observation that operations for hypertension are more effective in the young than in the old can be explained on the basis that the narrowing of the arterioles in this stage of the hypertensive process is largely functional. Inasmuch as the initiating mechanism responsible for the ultimate vascular narrowing has been stated as being in the central nervous system, it follows that any depression of its activity such as would be effected through denervation of the adrenals would depress the physiologic factors responsible for the hypertension. Only when persons with hypertension are in the state where depression of the mechanism for hypertension can account for the depression of blood pressure which follows operations for hypertension are they justified. The concept that hypertension *per se* is responsible for the degenerative changes of blood vessels is not supported by the experimental evidence. Thus, Goldblatt (1947) has found that dogs made hypertensive by renal blood vessel clamping, even after six years of hypertension, do not show arteriolar sclerosis such as is seen at autopsy in human beings with essential hypertension. The only significant change manifest in the arterioles of animals after prolonged hypertension is a thickening of the musculature of the arteriolar walls corresponding to the concentric muscular thickening of the left ventricle. Changes which characterize the arteriolar sclerosis of essential hypertension are to be attributed to the metabolic disturbances initiated by overaction of the hormone of the eosinophil cells of the hypophysis acting in combination with the associated overactivity of the adrenal cortex. The acute

degenerative changes in the arterioles found in the malignant phase of essential hypertension are reproducible in dogs when an excess of renin is released (Goldblatt, 1947, loc. cit.). From these facts it may be concluded that the lowering of blood pressure by the extensive denervation of the blood vessels cannot be expected to serve any useful purpose in preserving them from arteriolar sclerosis and denegeration.

SUMMARY

Evidence is presented to establish that a humoral mechanism, not overaction of the sympathetic nervous system, is the primary cause of essential hypertension.

A concept of the pathogenesis of essential hypertension is outlined. It is postulated on the basis of studies of Cushing's syndrome and of studies of hypothalamico-hypophysial relationships in the dog, that in man hypophysial eosinophil cell overaction with a resultant trophic stimulation of the adrenal cortex due to functional depression of the hypothalamic nuclei innervating the neural hypophysis is the primary cause of essential hypertension. The combined influence of the eosinophil cell—adrenal cortical hormone complex is to constrict the efferent glomerular arterioles of the kidney to result in a release of renin. The combined action of these three hormones causes hypertension and also the arteriolar sclerosis and degeneration ultimately associated with it. A constitutional susceptibility of the hypothalamus to depression and of the blood vessels to the constricting action of the hormones concerned in the causation of hypertension is deemed a prerequisite.

The role of epinephrine in hypertension is one of stimulation of the frontal lobes of the cerebral cortex. Its decrease by sympathectomy of the adrenal medulla is considered to be the mechanism whereby the production of hormones concerned in the pathogenesis of essential hypertension are decreased. Its decrease is responsible also in large measure for the relief from the symptoms of hypertension referable to the nervous system following sympathectomy of the adrenals.

Hypertension is regarded as a response of the body to a set of circumstances which threatens the adequate blood flow to the kidneys. A procedure is desirable only when it is capable of lessening the intensity of the humoral mechanism responsible for this deficiency of renal blood flow and when the consequent drop in blood pressure results from removal of the threatening circumstances rather than from an enlargement of the vascular bed.

In the treatment of hypertension, the only two organs capable of releasing humors concerned with the pathogenesis and symptomatology of hypertension and whose function can be modified by sympathectomy are the kidneys and the adrenals. It follows that any beneficial effect to be obtained by removal of portions of the sympathetic nervous system in the treatment of essential hypertension is to be obtained when such removal results in a denervation of the adrenals and the kidneys.

The removal of portions of the sympathetic nervous system more extensive than is required for denervation of the adrenals and the kidneys is unnecessary. It can have no influence on the causal mechanism of essential hypertension. The temporarily greater enlargement of the vascular bed effected thereby may cause a shunting of blood from the kidneys sufficient to impair their function and thereby, through the release of renin, accelerate the degenerative changes in the extra-renal blood vessels.

BIBLIOGRAPHY

- 1 Pickering, G. W.: The peripheral resistance in persistent arterial hypertension. *Clin. Sci.*, **2**, 209-235, 1935.
- 2 Goldring, W., H. Chassis, H. A. Ranges, and H. W. Smith: Effective renal blood flow in subjects with essential hypertension. *J. Clin. Investigation*, **20**, 637-653, 1941.
- 3 Koch, E., H. Mies, and M. Nordmann: Arterieller Hochdruck durch dauerausschaltung der Blutdruckzügler. *Ztschr. f. Krieslaufforsch*, **19**, 585-600, 1927.
- 4 Pickering, G. W., M. Kissin, and P. Rothchild: Relationship of carotid sinus mechanism to persistent high blood pressure in man. *Clin. Sc.*, **2**, 193-200, 1936.
- 5 Castleman, B., and R. H. Smithwick: The relation of vascular disease to the hypertensive state based on a study of renal biopsies from one hundred hypertensive patients. *J. A. M. A.*, **121**, 1256-1261, 1943.
- 6 Heinbecker, P.: Cushing's syndrome. *ANNALS OF SURGERY*, **124**, 252-261, 1946.
- 7 Heinbecker, P.: Pathogenesis of Cushing's syndrome. *Medicine*, **23**, 225-247, 1944.
- 8 Heinbecker, P., H. L. White, and D. Rolf: Experimental obesity in the dog. *Amer. J. Physiol.*, **141**, 566-570, 1944.
- 9 Heinbecker, P., D. Rolf, and H. L. White: Effects of extracts of the hypophysis, thyroid, and adrenal cortex on some renal functions. *Am. J. Physiol.*, **139**, 543-549, 1943.
- 10 White, H. L., P. Heinbecker, and D. Rolf: Some endocrine influences on renal function and cardiac output. *Am. J. Physiol.*, 1947, in press.
- 11 Heinbecker, P., H. L. White, and D. Rolf: The essential lesion in experimental diabetes insipidus. *Endocrinology*, **40**, 104-113, 1947.
- 12 Heinbecker, P., H. L. White, and D. Rolf: loc. cit., June, 1944.
- 13 Heinbecker, P.: loc. cit., Sept., 1944.
- 14 Heinbecker, P.: Studies on the sensitivity of smooth musculature to exogenous epinephrine. *Am. J. Physiol.*, **120**, 401-410, 1937.
- 15 Cannon, W. B.: *The wisdom of the body*. New York, Norton, 1932.
- 16 Heinbecker, P., and S. H. Bartley: Unpublished data.
- 17 Heinbecker, P.: Heart and median cardiac nerve of *Limulus polyphemus*. *Am. J. Physiol.*, **103**, 104-120, 1933.
- 18 Grimson, K. S.: Sympathectomy and circulation—anatomic and physiologic considerations and early and late limitations. *Surgery*, **19**, 277-298, 1946.
- 19 Goldblatt, H.: The renal origin of hypertension. *Physiol. Rev.*, **27**, 120-165, 1947.
- 20 Goldblatt, H.: loc. cit., 1947.

DISCUSSION.—DR. W. MCK. CRAIG, Rochester, Minn.: In any consideration of the surgical treatment of hypertension it is apparent the causative factors must be kept in mind. Hypertension in the concept of Richard Bright was caused by kidney involvement, but Sir William Gull suggested that narrowing of the arterioles played an important role. Ever since that time the cause of hypertension has been controversial. Doctor Heinbecker has presented a logical and comprehensive argument in favor of a minimal surgical removal of the sympathetic nervous system, but in contrast to his argument there are

some convincing reports in the literature that more extensive portions of the sympathetic nervous system should be removed. The challenge which the surgical treatment of hypertension must accept is based on a graph designed by the combined researches of the interest and the ophthalmologist in which the various groups are portrayed with the life expectancy. The groups range from I to IV depending upon the severity of the disease.

Any successful treatment of hypertension should alter the prognosis of the disease as portrayed in the delineation of the four groups. If by surgical intervention we can change the course of any group we have accomplished something, for that in itself is an acknowledgment of a change in prognosis.

The removal of the subdiaphragmatic portion of the splanchnic nerves and the ganglionated trunk has accomplished something in the treatment of hypertension, but more extensive resections of the splanchnic nerves and ganglionated trunks are being done with gratifying and interesting results. Time will prove how much of the sympathetic nervous system will have to be removed in order to influence the ultimate course of the hypertensive patient.

DR. PETER HEINBECKER, St. Louis (closing) : I thank Doctor Craig for his discussion. I do not wish to leave the impression that I consider the adrenals and kidneys to be the only organs which have to do with hypertension. They are the only ones whose function can be modified by sympathectomy. Also, I do not agree that there is any necessity for a more extensive operation to denervate the adrenals and the kidneys than that originally described by Craig and Adson. When I analyze the reports of various operators in this field I can see no difference in their results, if we take into consideration the age of the patient and the age of the disease.

THE PARADOX OF ACIDURIA IN THE PRESENCE OF ALKALOSIS CAUSED BY HYPOCHLOREMIA*

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THE PARADOX OF ACID URINE excretion in the presence of internal alkalosis caused by loss of gastric juice is a phenomenon that has been recognized by a few investigators especially interested in the acid-base balance, but remains unfamiliar to most physicians. In this day of sulfonamide therapy and whole blood transfusions, with the accompanying increasing frequency of occasions when alkalinization of urine is considered desirable, it becomes pertinent to study the details of a condition in which a low urine pH does not indicate either the desirability or the safety of alkali administration.

An acid urine in the presence of internal alkalosis may be encountered whenever there is severe loss of gastric juice, as by vomiting or gastric suction. The paradoxical combination that results is a plasma of abnormally high pH and bicarbonate content, accompanied by a urine of low pH and practically no bicarbonate content.

The lost gastric juice contains both hydrochloric acid and chlorides of Na and K, chiefly Na.^{1, 2} Loss of the sodium chloride and its equivalent of water causes dehydration. Loss of the hydrochloric acid causes part of the remaining plasma sodium chloride to be replaced by sodium bicarbonate, causing alkalosis to complicate the chloride loss and dehydration. In this condition, there is such a great depletion of body sodium salts that the kidneys cease to excrete sodium as either chloride or bicarbonate, despite the excessive plasma concentration of the bicarbonate. Urine lacking bicarbonate is acid.^{3, 4} The condition encountered, therefore, is one in which an internal alkalosis, caused by loss of hydrochloric acid, is accompanied by excretion of acid urine.

As first noted by Haden and Orr in 1923,⁵ bicarbonate administration in this condition is contraindicated because it increases the internal alkalosis and hastens the onset of tetany. If such a patient requires alkalinization of the urine, the preferable means is infusion of sodium chloride solution; this corrects the dehydration, sodium, and chloride deficit, decreases the internal alkalosis, and, at the same time, permits excretion of an alkaline urine; for alleviation of the body's deficit of sodium salts allows their excretion to be resumed. Of the excreted salts, part are in the form of bicarbonate, excreted from the excess present in the body, so that the urine pH rises. Sodium

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chloride infusion thus simultaneously alkalinizes the urine and restores the normal electrolyte pattern to the plasma and extracellular fluids of the body.

The concurrence of alkalosis and acid urine was produced experimentally in dogs in 1924 by Gamble and Ross,² who made a detailed study of the plasma and urine electrolyte changes and clearly discussed their significance. Hartmann and Smyth in 1926⁶ studied the condition as produced by vomiting in patients, noting the concurrence of bicarbonate excess and chloride deficit in the plasma accompanied by acid urine; they attributed the acidity of the urine to non-excretion of sodium bicarbonate, which, they believed, occurred when the total "concentration of crystalloids" in the plasma was diminished. Several other authors, quoted by McCance and Widdowson⁷ have noted the phenomenon, but it still appears not to have attained general recognition or understanding.

The present work supplements that of Gamble and Ross by providing additional studies of the experimentally induced condition, together with hour-by-hour observation of the blood and urine changes caused by sodium chloride and by sodium bicarbonate infusions. Control experiments have been done in which sodium chloride and sodium bicarbonate solutions were infused into normal dogs.

EXPERIMENTAL

Loss of gastric juice was produced in dogs by two methods: By the total gastric pouch method of Dragstedt,⁸ and by gastrostomy combined with ligation of the pylorus. At the time of the original operation, an episiotomy was performed to permit easy catheterization during periods of urine collection. Daily intravenous 5 per cent dextrose solutions were infused during the three to five days required for body chloride depletion. When the plasma chloride concentration fell to below 70 milliequivalents per liter (400 mg. NaCl per 100 cc.) the dogs were considered to be sufficiently depleted of chloride for this study. Moderate or severe alkalosis, as determined by abnormally high plasma bicarbonate concentration, was invariably produced.

The dogs were then given intravenous infusions of either 0.9 per cent NaCl or 1.3 per cent NaHCO_3 at a constant rate of about 1000 cc. per three hours. These solutions are, in electrolyte concentration, isotonic with plasma and contain 1.15 times the sodium concentration of normal plasma. However, the chloride content of the isotonic NaCl infusion is about 1.4 times that of normal dog plasma, and the bicarbonate concentration of the NaHCO_3 infusion is about six times that of the normal plasma. In addition to these electrolytes, all infusions contained 5 per cent dextrose to stimulate the excretion of adequate urine volumes for chemical analyses.

Heparinized jugular venous blood samples were collected at 30-60 minute intervals throughout each experiment, the samples for CO_2 analysis being taken under oil. Consecutive 15-30 minute period urine samples were collected from an indwelling catheter, with complete emptying of the bladder at the end of each period by air flushing except in experiments where urine was collected under oil for CO_2 analyses. Nembutal sedation was used only when necessary.

The following analytic methods were employed: plasma CO_2 content by the manometric method of Van Slyke and Neill,⁹ plasma and urine chlorides by Van Slyke and Hiller's modification of the titrimetric silver iodate method of Sendroy,¹⁰ urine pH by glass electrode, plasma and urine sodium and potassium by the flame photometer constructed by the Perkin-Elmer Corporation,¹¹ total plasma base by the electro-dialytic method of Malm (unpublished) based on the procedure of Adair and Keys,¹² plasma protein by the copper sulfate specific gravity method of Phillips et al,¹³ hematocrits by centrifugation.

For presenting and plotting the results, values for chloride, bicarbonate, sodium, total base, potassium, and R^2 are expressed in milliequivalents per liter of the ions, Cl , HCO_3 , Na , etc., rather than in grams of their respective salts. The use of milliequivalents facilitates comparison of the concentrations and changes in the different electrolytes. Normal dog plasma contains about 150 to 158 mEq/L of total base, the distribution being about 140 mEq/L of Na , 5 of Ca , 5 of K , and 3 of Mg . These cations are balanced by 105 to 115 mEq/L of Cl , 20–25 of HCO_3 , about 16 of protein, and the remainder by a residual sum, indicated by the symbol R , comprising SO_4 , HPO_4 , and unidentified anions. The sum of $\text{Cl} + \text{HCO}_3$ usually approximates the Na , except in starvation or dehydration when the R factor may be large. The only marked difference noted between the plasma electrolytes of man and the dog is that the chloride in the dog averages about 10 mEq/L higher than in man. The "isotonic" 0.9 per cent NaCl solution used for injections contains 154 mEq/L of Na and Cl , and the "isotonic" 1.3 per cent NaHCO_3 contains 154 mEq/L of Na and of HCO_3 .

The experiments presented below are selected as examples from 20 experiments that yielded similar results.

RESULTS

With only two exceptions in 20 experiments (experiments 3 and 4 in this paper) all the hypochloremic dogs (46–65 mEq/L plasma chloride concentration) showed the paradox of aciduria (urine pH 5–6) in the presence of moderate to severe alkalosis (plasma CO_2 35–51 mM/L.). Infusion of solutions of either sodium chloride or sodium bicarbonate into such dogs increased the urine pH. Sodium chloride infusion raised the urine pH in some cases as high as 7.8. Sodium bicarbonate infusions raised it as high as 8.4. Little or no rise of urine pH occurred when a hypochloremic dog was given intravenous 5 per cent dextrose solution, and sodium chloride infusion into normal dogs caused a fall in urine pH.

Experiment 1. The Effect of Infusing 0.9 Per Cent NaCl + 5 Per Cent Dextrose Intravenously Into Hypochloremic Dog. (Fig. 1a, 1b, 1c, 1d, Table I).

This experiment was conducted four days after gastrectomy and pyloric ligation of a 43-pound dog. Plasma analyses (see Table I) immediately prior to the saline infusion showed the dog to be in a state of extreme hypochloremia (plasma Cl 45.6 mEq/L), alkalosis (plasma HCO_3 49.9 mEq/L),* total base deficiency (plasma total base 137.3 mEq/L) and sodium deficiency (plasma sodium 125.5 mEq/L). Unfortunately, an

* HCO_3 concentrations in this paper are calculated from plasma CO_2 measurements by assuming a plasma pH of 7.5.

adequate pre-infusion urine sample was not obtained, for the dog had a tetanic convulsion and emptied her bladder just before the infusion was begun. The preliminary urine was undoubtedly acid, for the urine pH was 5.3 an hour after the infusion was started and the urine of almost all other hypochloremic dogs was acid.

During a 12-hour period, 4670 cc. of 0.9 per cent NaCl in five per cent dextrose solution was infused intravenously at a constant rate of 90-100 drops per minute. Small doses of intravenous nembutal controlled restlessness without putting the dog to sleep. Urine was collected in 30-minute periods under oil. Hourly jugular blood samples were also collected under oil. The infusion was continued 12 hours.

During the 12-hr. infusion 2853 cc. of urine were excreted (see Figure 1d), while 1817 cc., 38.9 per cent, of the infused water was retained. Of the 42 Gm. of NaCl infused, 11 Gm. were excreted and 31 Gm., or 74 per cent, were retained. 5.6 Gm. of NaHCO_3 (66.5 millimoles) were excreted during the experiment; this is equivalent to about 2.8 times the total grams of NaHCO_3 in the plasma of a normal dog of this animal's weight, and more than even this alkalotic animal had in her plasma at the beginning of the infusion. Obviously a good deal of the excreted sodium bicarbonate came from the interstitial fluids.

Figures 1a and 1b and table I show in detail the manner in which the intravenous sodium chloride infusion corrected both the hypochloremia and the alkalosis caused by gastric fluid loss. There is a striking return of the plasma acid-base balance to normal. Plasma Cl concentration rose from 45.6 mEq/L to the normal 110.0 mEq/L. Plasma bicarbonate fell from 49.9 mM/L to 27.7 mM/L. Plasma total base rose from 137.3 mEq/L to 154.0 mEq/L and plasma sodium from 125.5 to 150.0 mEq/L. Undeterminable anions,* Gambel's R factor² fell from 18.5 mEq/L to 3.1 mEq/L. During the last three hours of the infusion the hematocrit and the concentrations of protein, chloride, and bicarbonate in the plasma remained nearly constant at normal levels, indicating that the body's water and chloride deficits, and its bicarbonate excess, had been corrected.

The decrease in plasma bicarbonate concentration was partly due to the bicarbonate excretion discussed above; but in part it was attributable to dilution of the plasma and interstitial fluids with the infused 154 millimolar NaCl solution, which contained no bicarbonate and three times the plasma's Cl concentration. Dilution of the body's extracellular fluids with this chloride solution would obviously raise the Cl and lower the HCO_3 concentration. This dilution effect is shown by the rise of Cl and fall of HCO_3 in the plasma during the first three hours of the infusion, when practically no chloride or bicarbonate was being excreted.

Figures 1c and 1d and Table I show strikingly the way in which correcting the internal sodium chloride deficit released the excess bicarbonate for excretion, and in so doing raised the urine pH. When, after the third hour of infusion (1010 cc., 9 Gm. NaCl), excretion of sodium salts began to be accelerated, the first salt to be excreted was not chloride, but bicarbonate (Fig. 1c). From the third to the seventh hour the urine contained more bicarbonate than chloride. Then, plasma chloride having been doubled and plasma bicarbonate lowered by a third (Fig. 1a), urinary chloride concentration began to surpass bicarbonate.

The effect of the rise in urine bicarbonate in raising urine pH is shown by the parallelism of the pH and HCO_3 concentration curves in Figure 1c. Rise of urine bicarbonate concentration from 0.7 to its maximum of 44.1 millimoles per liter raised the pH from 5.3 to its maximum of 7.8. Thereafter, bicarbonate excretion continued in somewhat lower, but still rather high concentration, and urine pH continued at 7.42-7.68.

* R factor, the undeterminable anions, is determined by subtracting the sum of base combined with Cl, HCO_3 , and proteins from the total base. In these experiments the base combined with proteins is calculated: $B \text{ protein} = 0.234 \times \text{Gm. per cent protein}$ assuming a normal A/G ratio of 1.8 (14). Total base determinations, by the electro-dialysis method employed, do not include Mg^{++} .

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Chloride excretion was insignificant until the plasma chloride concentration reached 80 mEq/L. As the plasma chloride concentration rose above 80 mEq/L the rate of chloride excretion rose with it; the threshold level of plasma chloride was therefore about 80 mEq/L in this experiment.

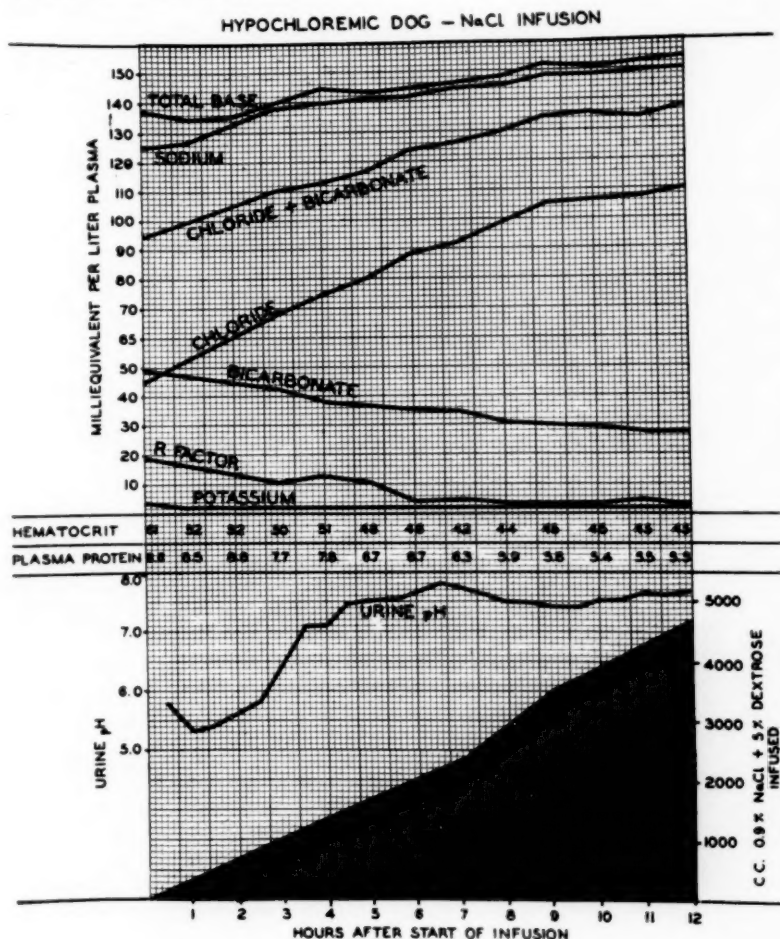


FIG. 1A.—Showing the effect of 0.9 per cent NaCl + 5 per cent dextrose infusion on the plasma electrolyte pattern of a hypochloremic alkalotic dog. Note that, despite the fall in plasma bicarbonate concentration the urine pH rises as the body NaCl deficit is corrected.

At the start of this experiment the plasma potassium concentration was 3.9 mEq/L (normal 4.5–5.0 mEq/L). This potassium deficit is consistent with the observations of Gambel and McIver¹ that cat and dog gastric juice contains up to 50 mg. per cent of potassium and with the observation of Elkinton and Winkler¹⁵ that dehydration in itself is likely to diminish the potassium supply of the body.

Within an hour after the start of the sodium chloride and dextrose infusion the plasma potassium fell to 2.0 mEq/L and thereafter it remained below 2.7 mEq/L. Similar washing out of plasma potassium by infused sodium chloride solution has been reported in experiments by Flock¹⁶; and recently Holler¹⁷ and Martin and Wertman¹⁸ have clinically observed reduction of plasma potassium to paralytic levels in diabetic

TABLE I
HYPOCHLOREMIC DOG
0.9% NaCl + 5% DEXTROSE I. V. INFUSION

Procedure			Plasma										
Minutes after start of infusion	Volume infused (cc)	NaCl infused (Gm.)	Blood and Urine Samples	Sample	Hemato- crit %	Total Protein Gm. %	Cl mEq/L	HCO ₃ mM/L	Cl+HCO ₃ mEq/L	R	Na mEq/L	K mEq/L	Total base mEq/L
-15	0			Bc	60.5	9.61	45.6	49.9	95.5	18.5	125.5	3.9	137.3
0	0	1.8	U ₀										
30	200		U ₁										
60	360	3.2	B ₁	B ₁	52.2	8.50	53.6	lost	127.5	2.0	134.9
90	615	5.5	U ₃										
125	700	6.3	B ₂	B ₂	52.4	8.61	60.5	lost	133.0	...	135.7
150	850	7.6	U ₃										
180	1010	9.1	B ₃	B ₃	50.4	7.73	68.2	42.8	111.0	10.2	138.5	2.1	140.0
210	1180	10.6	U ₇										
240	1360	12.2	B ₄	B ₄	51.3	7.80	75.0	38.3	113.3	12.6	140.0	2.1	144.8
270	1500	13.5	U ₉										
300	1680	15.1	B ₅	B ₅	47.5	6.67	80.0	36.9	116.9	10.4	141.5	2.7	143.5
330	1860	16.7	U ₁₁										
360	B ₆	B ₆	47.5	6.67	88.8	35.3	124.1	4.0	142.0	2.2	141.3
390	2190	19.7	U ₁₃										
420	2370	21.3	B ₇	B ₇	46.5	6.28	92.0	34.4	126.4	4.5	144.5	2.5	146.2
450	2680	24.1	U ₁₅										
480	2940	26.4	B ₈	B ₈	43.8	5.90	99.0	30.8	129.8	3.7	145.5	2.2	147.8
520	U ₁₇										
550	3520	31.7	B ₉	B ₉	44.9	5.83	105.5	29.1	134.6	3.6	148.5	...	152.4
570	3660	32.9	U ₁₈										
600	3870	34.8	B ₁₀	B ₁₀	44.6	5.35	106.5	29.0	135.5	3.2	148.5	2.2	151.7
630	4130	37.1	U ₂₁										
660	4290	38.6	B ₁₁	B ₁₁	44.5	5.54	107.1	27.4	134.5	4.6	149.0	2.2	152.6
690	4470	40.2	U ₂₃										
720	4670	42.0	B ₁₂	B ₁₂	44.7	5.50	110.0	27.7	137.7	3.1	150.0	2.2	154.0

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TABLE I (cont.)
HYPOCHLOREMIC DOG
0.9% NaCl + 5% DEXTROSE I. V. INFUSION
Urine

Sample	Volume		pH	Chloride			Sodium			HCO ₃			NaHCO ₃ Excretion mg/period
	cc./period	cc./min.		Concen- tration mEq/L	Excretion mEq/min.	NaCl Excretion mg/period	Concen- tration mEq/L	Excretion mEq/min.	CO ₂ mM/L	Concen- tration mEq/L	Excretion mEq/Min.		
Uc	3												
U ₁	15	0.50	5.9	0	0	0	4	0.002	1.9	0.7	0.0	1	
U ₂	41	1.36	5.3	0	0	0	4	0.005	1.4	0.2	0.0	1	
U ₃	54	1.80	5.4	0.5	0.001	2	13	0.023					
U ₄													
U ₅	152	2.54	5.8	0.5	0.001	4	17	0.043	1.8	0.6	0.002	10	
U ₆	96	3.20	6.4	0.5	0.002	4	26	0.083	5.2	3.5	0.001	28	
U ₇	93	3.10	7.1	1.5	0.005	8	39	0.121					
U ₈	119	3.97	7.1	3.0	0.012	21	48	0.190	26.3	23.9	0.095	425	
U ₉	103	3.44	7.45	3.4	0.012	21	48	0.165					
U ₁₀	116	3.87	7.54	5.6	0.022	38	52	0.201	32.9	31.6	0.122	582	
U ₁₁	130	4.34	7.56	14.2	0.062	76	65	0.282	40.2	38.9	0.194	910	
U ₁₂	148	4.94	7.65	26.5	0.131	231	70	0.345					
U ₁₃	66	2.20	7.80	36.8	0.081	142	74	0.163	45.0	44.1	0.147	616	
U ₁₄	100	3.33	7.76	42.2	0.147	246	78	0.252	26.4	25.2	0.175	702	
U ₁₅	125	4.13	7.63	57.2	0.236	418	87	0.363					
U ₁₆	206	6.87	7.50	68.0	0.467	806	87	0.598					
U ₁₇	172	4.30	7.49	89.5	0.385	900	94	0.404	20.4	19.5	0.207	803	
U ₁₈	318	10.60	7.42	115.0	1.220	2140	104	1.110					
U ₁₉	92	4.60	7.43	118.5	0.543	638	130	0.598	20.9	20.1	0.105	421	
U ₂₀	157	5.24	7.52	121.9	0.639	1119	144	0.754					
U ₂₁	132	4.40	7.54	124.3	0.547	959	152	0.669	23.2	22.5	0.102	507	
U ₂₂	136	4.54	7.68	128.5	0.584	1022	152	0.690					
U ₂₃	144	4.80	7.61	130.0	0.624	1095	152	0.730	25.3	24.6	0.106	577	
U ₂₄	135	4.50	7.65	134.0	0.643	1113	152	0.684					
	2853 cc.					11.0 Gm.						5.6 Gm.	

patients treated with large infusions of intravenous dextrose and sodium chloride. It is possible that some of the potassium is deposited into the liver and muscle with glycogen formed from the infused dextrose, as postulated by Fenn.¹⁰

That paralysis did not develop may be due to the simultaneous loss of calcium. Though direct calcium determinations were not made in this experiment, the difference between total base and the $\text{Na} + \text{K}$ in the plasma during the infusion fell so low that it appears that calcium must have fallen much below the normal 5 mEq/L. Since neither tetany nor paralysis occurred, the possibility suggests itself that simultaneous calcium

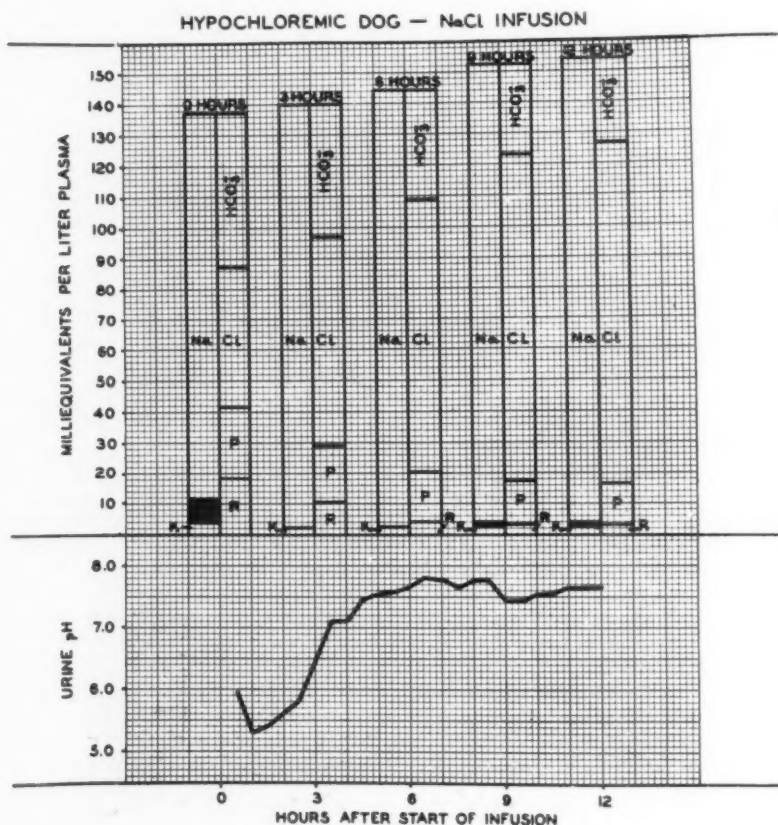


FIG. 1B.—Showing the effect of 0.9 per cent NaCl + 5 per cent dextrose infusion on the plasma electrolyte pattern of a hypochloremic alkalotic dog. Note that, despite the fall in plasma bicarbonate concentration, the urine pH rises as the body NaCl deficit is corrected. Also note the decrease in concentrations of cations other than sodium.

and potassium deficiency neutralized each other with regard to effect on muscle tone.

From this experiment, and from the clinical observations of others, it would seem advisable that a balanced electrolyte solution containing not only Na, but also Ca, K and Mg should be used when large electrolyte infusions are given.

This 43-pound dog excreted 5.6 Gm. of NaHCO_3 during the 12 hr. NaCl solution infusion. This bicarbonate excretion is equivalent to about 20 Gm. for a 70-kg. man. Since the body contained at least this much excess bicarbonate, it is apparent that bicarbonate administration was not indicated, despite the acid urine.

ACIDURIA WITH ALKALOSIS

Experiment 2. The Effect of Infusing 0.9 Per Cent NaCl + 5 Per Cent Dextrose Intravenously Into Hypochloremic Dog. (Fig. 2, Table II).

This experiment practically duplicates the first three hours of Experiment 1, except that the initial plasma chloride deficit and bicarbonate excess were not quite so great (Cl 56.6 mEq/L, HCO_3 37 mM/L, compared with Cl 45.6 and HCO_3 49.9 in Experiment 1; sum of chloride plus bicarbonate nearly the same in both). The infusion, as that of the

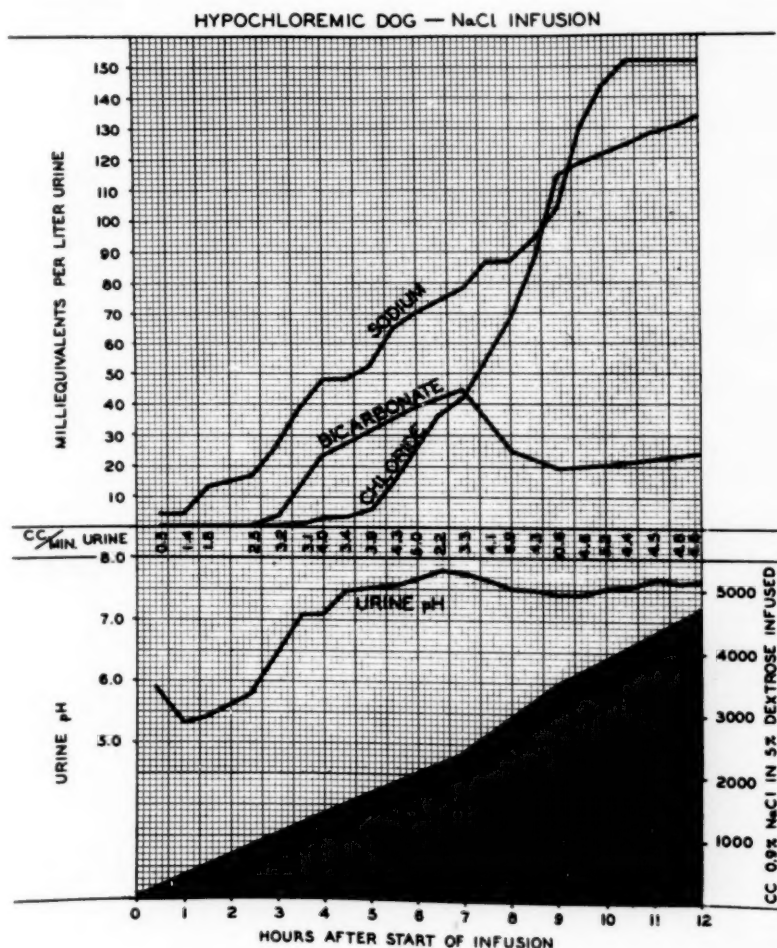


FIG. 1C.—Showing the effect of 0.9 per cent NaCl + 5 per cent dextrose infusion on the urine NaCl and NaHCO_3 concentrations of a hypochloremic alkalotic dog. Note that NaCl infusion frees a large amount of NaHCO_3 for excretion, and that urine pH parallels urine NaHCO_3 concentration.

first three hours of dog one, was insufficient to start significant excretion of water, chloride, or bicarbonate, the urinary HCO_3 concentration at the end of the three hours being sufficient only to raise the pH to 6.52. The initial dehydration of the dog is shown by the fact that during the three hours only eight per cent of the infused water was excreted. The partial correction of the plasma electrolyte picture (fall in HCO_3 , rise in Cl and Na) is attributable, as in the first three hours of Experiment 1, to dilution of plasma and interstitial fluids with the infused 154 millimolar NaCl solution.

TABLE II
HYPOCHLOREMIC DOG
0.9% NaCl + 5% DEXTROSE I. V. INFUSION

Procedure			Plasma					
Minutes After Start of I infusion	Volume Infused (cc.)	Blood and Urine Samples	Sample	Hematocrit	CO ₂ mM/L	Cl mEq/L	CO ₂ + Cl mEq/L	Na mEq/L
0	0	Bc Uc	Bc		39.5	56.6	96.2	111
35	160	B ₁	B ₁	25	35.4	61.3	96.7	111
60	260	B ₂ U ₁	B ₂	24	34.7	62.3	97.0	109
90	400	B ₃	B ₃	20	34.2	65.8	100.0	112
120	570	B ₄ U ₂	B ₄	19	32.0	69.4	101.4	114
150	760	B ₅	B ₅	22	33.6	73.3	106.9	116
180	890	B ₆ U ₃	B ₆	21	31.0	76.0	106.0	116

Sample	Volume		Urine Chloride		Sodium		NaCl mg./period
	cc./period	pH	Concentration Gm./L	Excretion Mg./min.	CO ₂ mM/L	Concentration Gm./L	
Uc	12	5.97	0	0	2.68	0.02	0
U ₁	18	6.10	0	0	2.28	0.03	0
U ₂	37	6.00	0	0	2.18	0.08	1.4
U ₃	67	6.52	0.04	0.026	3.70	0.05	8.2
							10.8 mg
							1.56 mg

ACIDURIA WITH ALKALOSIS

Experiment 2 serves for comparison with Experiment 3 in which isotonic NaHCO_3 instead of NaCl was infused. In both experiments the initial dehydration, plasma Cl deficit and HCO_3 excess were nearly the same.

Experiment 3. The Effect of Infusing 1.3 Per Cent NaHCO_3 + 5 Per Cent Dextrose Intravenously Into Hypochloremic Dog. (Fig. 3, Table III).

In this experiment a salt depleted dehydrated dog was infused with an isotonic solution of sodium bicarbonate instead of sodium chloride. 900 cc. of 1.3 per cent sodium bicarbonate in five per cent dextrose solution were given during a three-hour period.

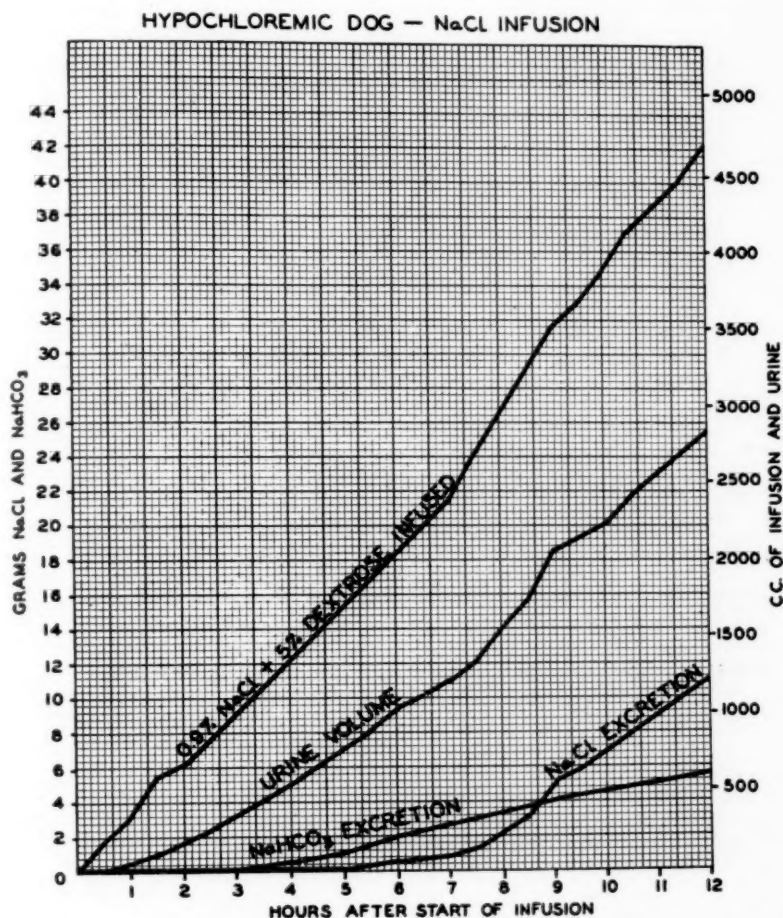


FIG. 1D.—Showing the total grams of NaCl and NaHCO_3 excreted by a hypochloremic alkalotic dog receiving intravenous 0.9 per cent NaCl + 5 per cent dextrose. Note that NaCl infusion frees a large quantity of NaHCO_3 for excretion.

Water excretion was more accelerated than in the previous experiments, the total urine excretion being 73 per cent of the infused solution, compared with eight per cent in Experiment 2. The diuresis was accompanied by a rapid increase in sodium salt excretion. The sodium excretion here was almost chloride free. The high bicarbonate content of the urine raised the pH above eight during most of the experimental period.

In this experiment, with sodium bicarbonate infusion, the infused sodium salt and water were less completely retained than in the preceding experiments where sodium chloride solution was infused. Of the sodium chloride infused during the previous experiments, only 0.0 to 0.1 per cent was excreted whereas of the sodium bicarbonate infused in this experiment, 38 per cent was excreted before the experiment finished.

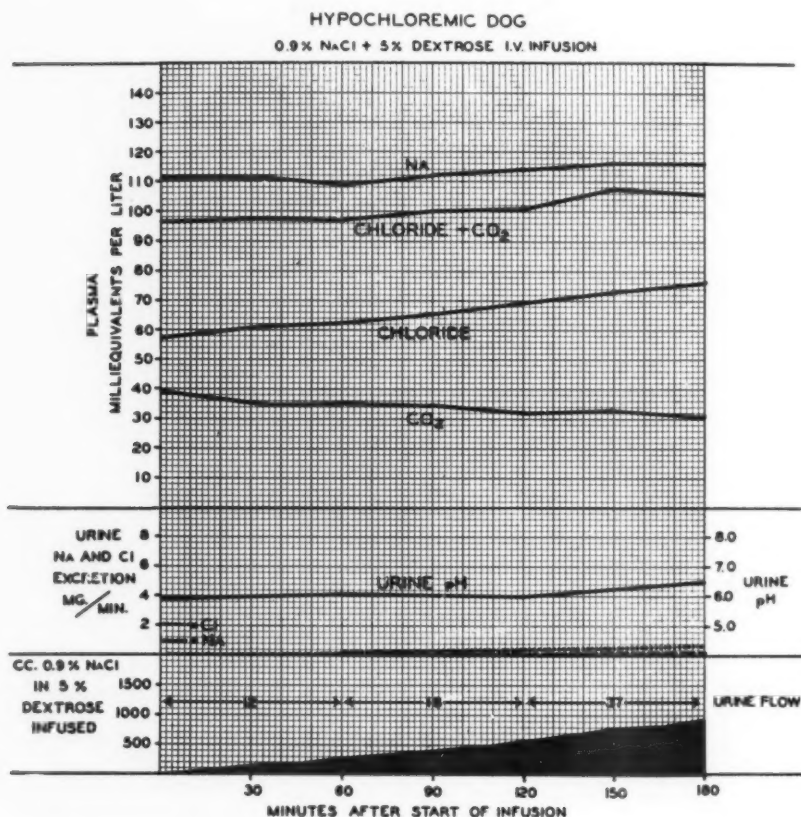


FIG. 2.—Showing the early effects of 0.9 per cent NaCl + 5 per cent dextrose infusion into a hypochloremic alkalotic dog. Note the almost complete retention of the infused saline causing plasma electrolyte changes by simple dilution and no changes in the urine.

It appears that the refusal of the kidneys to retain the infused bicarbonate may be attributable to the fact that the plasma bicarbonate concentration had already been raised by gastric hydrochloric acid loss to twice the normal level, and retention of bicarbonate would have increased the excess of that salt already present in the alkalotic organism.

The hypochloremic alkalotic plasma electrolyte pattern became even more marked during the bicarbonate infusion; chloride concentration fell, CO₂ rose, total base and R factor changed little. Thus the electrolyte imbalance was aggravated. This increasing alkalosis was accompanied by repeated convulsions necessitating intravenous nembutal.

The results indicate the undesirability of infusions of sodium bicarbonate in the state of hypochloremic alkalosis, even when accompanied by an initially acid urine.

ACIDURIA WITH ALKALOSIS

TABLE III
HYPOCHLOREMIC DOG
1.3% NaHCO₃+5% DEXTROSE I. V. INFUSION

Minutes after Start of Infusion	Procedure	Blood and Urine Samples	Plasma					URINE				
			Sample	Hematocrit %	Total Protein Gm. %	Cl mEq/L	HCO ₃ mEq/L	Cl+HCO ₃ mEq/L	Total Base mEq/L	R		
0		Bc	Uc	58.4	7.8	60.1	34.2	94.3	129.2	15.9		
30		B ₁	U ₁									
45	200	B ₁	U ₁	52.5		55.0	40.7	95.7				
60		B ₂	U ₂									
65	310	B ₂	U ₂	52.0		54.8	42.2	97.0				
90	420	B ₃	U ₃	48.7	6.2	52.9	41.6	94.5	129.5	19.9		
120	600	B ₄	U ₄	48.3	5.9	52.6	47.0	99.6	128.2	14.3		
127		B ₄	U ₄									
150	750	B ₅	U ₅	48.9	6.0	51.9	48.4	100.3	131.2	16.3		
165		B ₅	U ₅	50.4	5.8	53.0	50.9	103.9	129.4	11.4		
180	900	B ₆	U ₆									
557												
Sample	Volume cc./period	pH	Chloride		Total NaCl		Sodium		HCO ₃		Total NaHCO ₃	
			Concentration mEq/L	Excretion mEq/min.	Excretion mg./period	Concentration mEq/L	Excretion mEq/min.	Concentration mM/L	Excretion mM/min.	Concentration mM/L	Excretion mM/min.	Concentration mM/L
Uc	95	6.40	0	0	0	8.7	0.000	2.2	0.000	1.1	0.000	0.27
U ₁	98	7.53	0	0	0	57.4	0.182	35.3	0.108	34.0	0.108	0.58
U ₂	111	8.08	1.1	0.004	6.3	74.4	0.243	71.3	0.230	70.5	0.230	0.40
U ₃	146	7.89	0.9	0.003	5.9	78.3	0.290	43.9	0.169	43.2	0.169	0.89
U ₄	113	8.02	1.2	0.006	10.3	98.3	0.479	73.6	0.354	72.7	0.354	0.94
U ₅	98	8.11	2.2	0.008	14.6	118.2	0.446	99.3	0.371	98.5	0.371	1.36
U ₆	661	8.16	2.3	0.008	13.2	130.5	0.427	165.1	0.538	164.7	0.538	4.4Gm.
	661 cc.				50.3 mg.							

TABLE IV
HYPOCHLOREMIC DOG
5% DEXTROSE IN WATER I. V. INFUSION

Minutes After Start of Infusion	Procedure Volume Infused (cc.)	Blood and Urine Samples	Plasma				Na mEq/L
			Sample	Hematocrit	Cl mEq/L	CO ₂ mM/L	
0	0	Be U _c	B _c	45.7	64.6	40.1	120
25	110	B ₁ U ₁	B ₁	43.2	61.0	39.4	115
60	290	B ₂ U ₂	B ₂	42.0	58.6	37.2	112
90	430	B ₃ U ₃	B ₃	40.8	57.4	35.0	109
120	620	B ₄ U ₄	B ₄	41.8	56.4	37.9	103
150	790	B ₅ U ₅	B ₅	—	54.9	37.5	92.4
180	910	B ₆ U ₆	B ₆	39.0	54.1	37.7	91.8

URINE				Chloride		Sodium	
Sample	cc /period	Volume cc./min.	pH	Gm./L Concentration	mg/min. Excretion	Gm./L Concentration	mg/min. Excretion
U _c	—	—	6.72	0.025	—	0.048	—
U ₁	16	0.64	6.51	0.039	0.02	0.050	0.03
U ₂	58	1.7	6.54	0	0	<0.010	<0.02
U ₃	45	1.5	6.90	0.014	0.02	<0.010	<0.02
U ₄	88	2.9	6.90	0.007	0.02	<0.010	<0.02
U ₅	61	2.0	7.15	0.007	0.01	<0.010	<0.02
U ₆	54	1.8	7.19	0.019	0.03	<0.010	<0.02
—	—	—	—	—	—	—	—
—	322 cc.	—	—	—	—	—	5.6 mg.

ACIDURIA WITH ALKALOSIS

TABLE V
NORMAL DOG
0.9% NaCl + 5% DEXTROSE I. V. INFUSION

Procedure			Plasma									
Minutes After Start of Infusion	Volume Infused (cc.)	Blood and Urine Samples	Sample	Hematocrit %	Total Protein Gm. %	Cl mEq/L	CO ₂ mM/L	Cl + CO ₂ mEq/L	URINE			
									Chloride		Sodium	
Sample	cc./period	pH	Gm/L Concentration	mg/min. Excretion	NaCl Excretion mg./period	Gm/L Concentration	mg/min. Excretion	CO ₂ mM/L	Gm/L Concentration	mg/min. Excretion	NaHCO ₃ Excretion mg./period	NaHCO ₃ Excretion mg./period
Uc	32	6.5	2.4	2.57	1.4	1.50	4.9	0.29	0.31
U ₁	41	5.7	0.6	0.82	41.4	0.2	0.27	1.72	0.04	0.06	1.72	1.72
U ₂	18	5.8	0.8	0.48	24.2	0.1	0.06	1.08	0.03	0.02	0.61	0.61
U ₃	14	5.5	4.6	2.16	106.1	0.9	0.42	0.81	0.02	0.01	0.24	0.24
U ₄	20	4.8	7.7	5.08	253.0	2.3	1.52	0.78	0.00	0.00	0.08	0.08
U ₅	30	4.7	7.9	7.90	391.0	2.7	2.70	0.74	0.00	0.00	0.09	0.09
U ₆	79	4.6	5.3	13.92	699.0	1.5	3.95	0.96	0.00	0.00	0.16	0.16
234 cc.												2.9 mg.

Experiment 4. The Effect of Infusing 5 Per Cent Dextrose In Water Into Hypochloremic Dog. (Fig. 4, Table IV).

This experiment serves as control for those in which NaCl plus dextrose or NaHCO_3 plus dextrose was infused. The dog received 910 cc. of solution in three hours and excreted 322 cc. of urine, or 35 per cent of the infused volume. The effects on plasma Cl , HCO_3 and Na concentrations are those of simple dilution by the retained water (hematocrit fell from 45.7 to 39.0 per cent). Excretion of Cl and Na were negligible. The urinary pH was raised only 0.4.

This control experiment shows that the rise in urine pH in Experiments 1, 2, and 3 was not the result of the glucose diuresis.

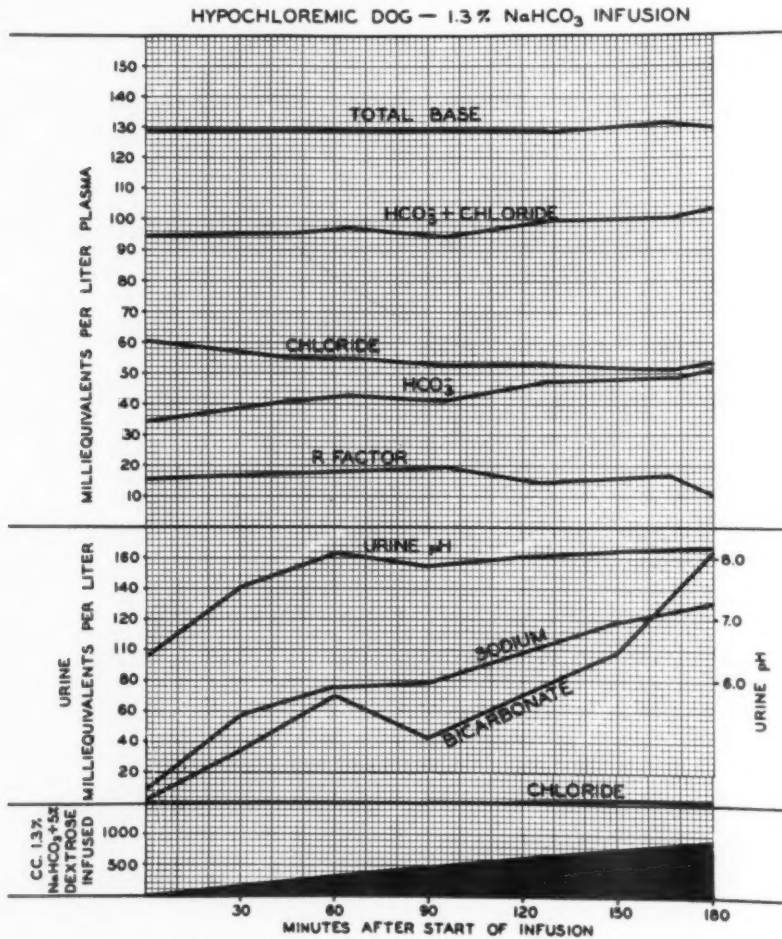


FIG. 3.—Showing the effects of 1.3 per cent (isotonic) NaHCO_3 + 5 per cent dextrose infusion into a hypochloremic alkalotic dog (compare with Fig. 2). Note the undesirable aggravation of the plasma anion imbalance and the failure to retain the infused solution.

This experiment shows: (1) that dextrose solution infused without salt into a dehydrated animal is not well retained (35 per cent of infused fluid was excreted during the three-hour infusion compared with eight per cent when 0.9 per cent NaCl was infused), (2) that such infusion does not correct the plasma chloride deficit nor, to a

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TABLE VI
NORMAL DOG
1.3% NaHCO₃ 5% DEXTROSE I. V. INFUSION

Procedure			Blood and Urine			Plasma		
Minutes after Start of Infusion	Volume Infused (cc.)	Samples	Sample	Hematocrit %	Cl mEq/L	Cl mM/L	Cl+CO ₂ mEq/L	
0	0	Bc	Bc	32.7	116.0	23.6	139.6	
60	360	B ₁ U ₁	B ₁	29.3	109.8	28.5	138.3	
120	680	B ₂ U ₂	B ₂	29.5	107.3	35.1	142.4	
187	1020	B ₃ U ₃	B ₃	30.5	104.1	38.7	142.8	
240	1270	B ₄ U ₄	B ₄	30.4	104.1	37.6	141.7	
300	1570	B ₅ U ₅	B ₅	29.3	102.2	38.2	140.6	
340	1770	B ₆ U ₆	B ₆	28.9	102.5	40.7	143.2	

URINE					
Sample	Volume		Chloride		NaCl Excretion mg./period
	cc./period	cc./min.	Gm/L Concentration	mEq/min. Excretion	
Uc	..33
U ₁	16	0.27	3.6	0.03	93.5
U ₂	70	1.17	2.4	0.08	272
U ₃	143	2.14	1.7	0.10	395
U ₄	220	4.16	1.4	0.16	500
U ₅	252	4.20	1.2	0.15	492
U ₆	173	4.33	0.74	0.09	207
					1.86 Gm.
					874 cc.

Sodium			HCO ₃			NaHCO ₃ Excretion mg./period
Gm/L Concentration	mEq/min. Excretion	CO ₂ mM/L	gm/L Concentration	mEq/min. Excretion		
....	22.8	
5.5	0.06	136	8.2	0.03	180	
5.1	0.26	181	10.9	0.21	1050	
3.9	0.36	140	8.5	0.30	1670	
3.7	0.67	141	8.5	0.58	2440	
3.4	0.62	143	8.6	0.60	3030	
3.8	0.72	154	9.3	0.66	2220	
					10.6 Gm.	

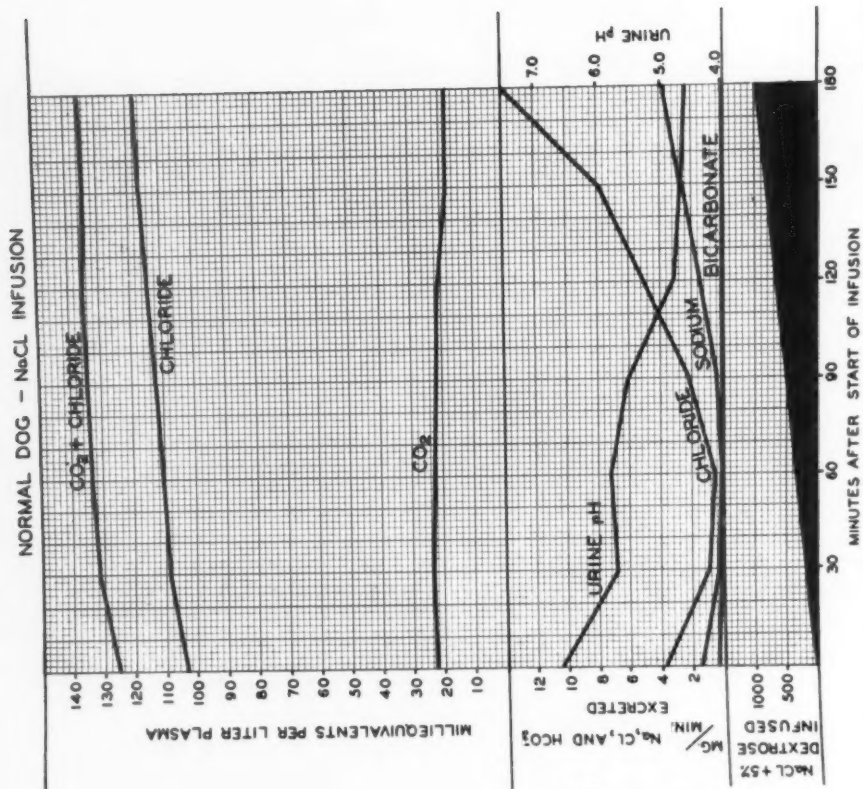


Fig. 5.—Control experiment showing the effects of 0.9 per cent NaCl + 5 per cent dextrose infusion into a normal dog. Compare with Figures 1, 2, and 3. Note the fall in urine pH caused by a dilution of the plasma bicarbonate to below its renal threshold concentration.

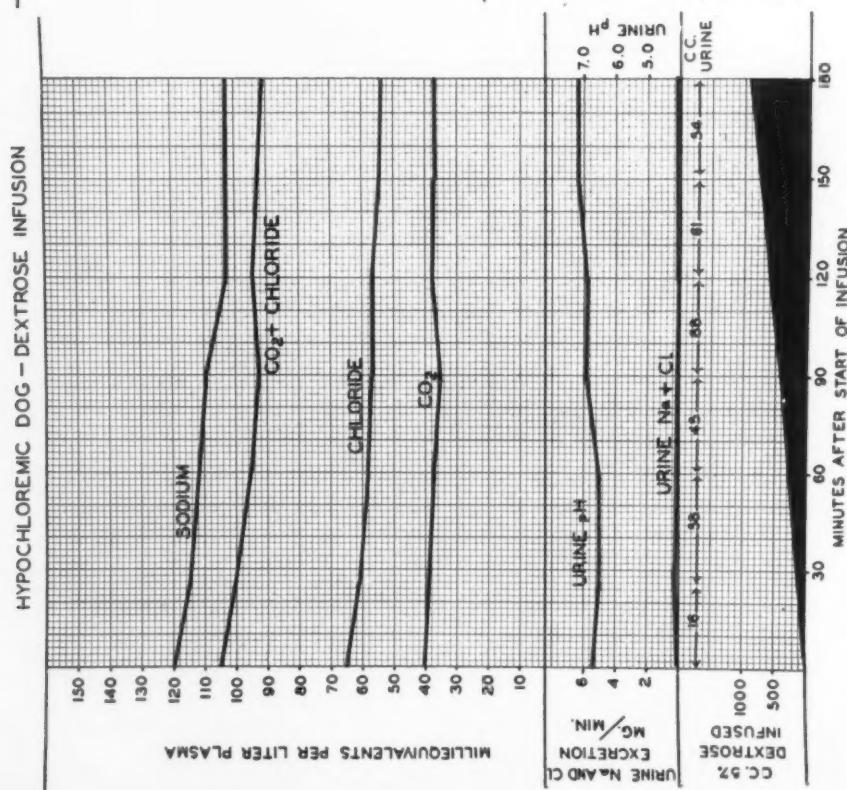


Fig. 4.—Control experiments showing the effects of five per cent dextrose infusion into a hypochloremic alkalotic dog. Note that the resultant diuresis does not raise the urine pH, and that the urinary effects of the NaCl dextrose and NaHCO₃ dextrose infusions in Experiments 1, 2, and 3 are not attributable to the infused dextrose.

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significant extent, the bicarbonate excess, and (3) that it does not accelerate bicarbonate excretion sufficiently to cause a marked rise in urinary pH.

Experiment 5. The Effect of Infusing 0.9 Per Cent NaCl + 5 Per Cent Dextrose Into Normal Dog. (Fig. 5, Table V). (Control Experiment).

In this experiment 980 cc. of a solution containing 0.9 per cent NaCl plus five per cent dextrose were infused intravenously during three hours, as in Experiments 1 and 2. Figure 5 shows the effects of diluting the plasma with 0.9 per cent sodium chloride

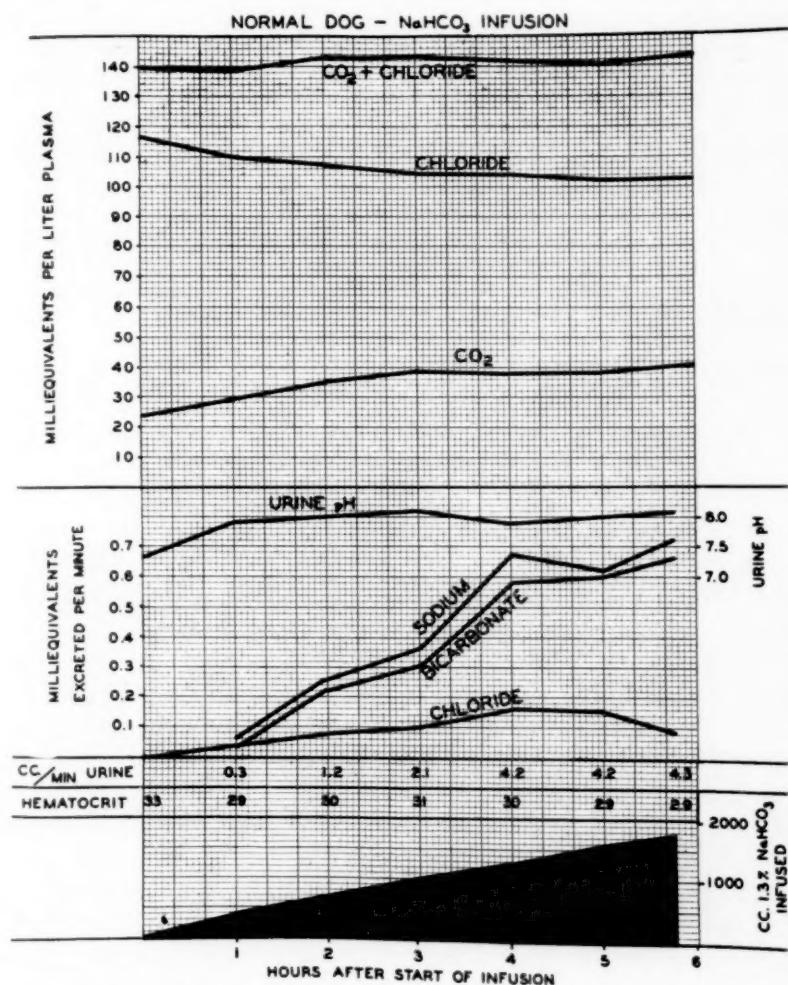


FIG. 6.—Control experiment showing the effects of 1.3 per cent (isotonic) NaHCO_3 + 5 per cent dextrose infusion into a normal dog.

solution (Cl concentration 154 mEq/L and CO_2 concentration 0); plasma chloride concentration rose 15 mEq/L and CO_2 fell from 22.9 to 17.5 mM/L.

Urine chloride concentration, after a peculiar fall in the first period, increased and reached 7.9 Gm/L, with a parallel increase in the rate of chloride excretion. The bicarbonate excretion rapidly fell to zero and remained there while the urine pH fell from 6.5 to 4.6. In this and other similar experiments the kidney bicarbonate threshold was

at about 20 mEq/L. Pitts,²⁰ under somewhat different conditions, found the bicarbonate threshold at about 25 mEq/L.

Comparison of this experiment with those of the hypochloremic dog reveals opposite effects on the urine pH. In the initially normal dog the urine pH falls as the plasma bicarbonate is decreased. In the hypochloremic dog, urine pH rises as the increasing plasma sodium chloride content releases the excess plasma sodium bicarbonate for excretion.

Experiment 6. The Effect of Infusing 1.3 Per Cent NaHCO_3 + 5 Per Cent Dextrose Into Normal Dog. (Fig. 6, Table VI).

This dog received 1000 cc. of isotonic sodium bicarbonate solution during the first three hours (compare Experiments 2 to 5) and 770 cc. more during the next three hours. The dog, at the start, was apparently somewhat dehydrated, as indicated by the low initial urinary volume and Cl and Na excretion (Fig. 6). The first three hours the dog excreted 2.9 Gm. of NaHCO_3 , or 22 per cent of the amount at that time infused. At the end of the six-hour infusion, 10.7 Gm. of NaHCO_3 had been excreted, or 46 per cent of the total 23 Gm. infused.

The chief difference in results from those of NaHCO_3 infusion into the hypochloremic dog of Experiment 3, is that in the normal dog the NaHCO_3 infusion caused a significant increase in urinary chloride excretion, although less than in bicarbonate output. The hypochloremic dog (Experiment 3) excreted practically no chloride. Only the hypochloremic dog suffered convulsions during bicarbonate infusion.

DISCUSSION

The results presented confirm Hartmann⁶ and Gamble² in showing that *loss of gastric juice produces a condition of dehydration, hypochloremia and alkalosis that is paradoxical in that severe alkalosis (high plasma bicarbonate) is accompanied by excretion of acid urine.* The results also confirm Hartmann and Gamble to the effect that *dehydration, deficit in plasma Cl and Na, and excess of plasma bicarbonate, can be corrected by infusion of isotonic NaCl solution, which also causes the urine to become alkaline. The initial acidity of the urine does not indicate the desirability of alkali therapy, which would increase the internal alkalosis.* The results emphasize the importance of guiding the therapy in this condition by determination of plasma CO_2 and chloride. Estimations of hematocrits and plasma protein concentration as indicators of dehydration are also valuable; each may be 50 per cent above normal.

The paradoxical low pH of the urine in the face of internal alkalosis is attributable to the almost complete absence of bicarbonate from the urine. The deficit of sodium salts in the body is so great that the kidneys stop excretions of both NaCl and NaHCO_3 . As shown by Gamble³ and Sendroy, Seelig and Van Slyke,⁴ the urine always contains free H_2CO_3 in equal or greater concentration than the blood, so that if no NaHCO_3 is excreted, the pH will fall to that of a solution of such H_2CO_3 concentration, viz., about pH 5.

Infusion of NaCl, by correcting the body's deficit of sodium salts, permits excretion of NaHCO_3 and rise of urine pH. One encounters another apparent paradox in that infusion of neutral NaCl solution causes excretion of alkaline, bicarbonate-containing urine.

The results of Experiment 1 and 2, with infusion of NaCl into dogs

suffering from dehydration, chloride deficit and alkalosis from loss of gastric fluid also show that:

1. In severe dehydration from loss of gastric juice, NaCl infusion corrects the abnormalities of the plasma electrolyte pattern by three mechanisms: (a) the lost sodium chloride and water are replaced, (b) the excessive bicarbonate concentration in plasma and interstitial fluids is decreased by dilution with the infused chloride solution and (c) plasma bicarbonate is further lowered by excretion of bicarbonate in the urine in large amounts.
2. To complete the correction of the plasma pattern, large amounts of NaCl solution must be infused. To restore plasma Cl and HCO_3 to approximately normal concentration, the 20-kg. dog in Experiment 1 required 3 liters of 0.9 per cent NaCl solution, or 150 cc. per kg., which was infused during the first eight hours.
3. Reappearance of chloride in the urine could not be used as indication that enough saline had been infused to correct the plasma electrolyte pattern. In Experiment 1, after infusion of 100 cc. of 0.9 per cent NaCl per kg., chloride concentration in the urine reached 20 mEq/L. (0.71 Gm. per liter) when plasma chloride was still only 90 mEq/L (compared with normal dog's 110-120) and plasma bicarbonate was 36 mM/L (normal 20-25). It was only towards the end of the infusion, when chloride concentration in the urine reached about 100 mEq/L (6 Gm. NaCl per liter), that plasma values approached normal (Cl 105 mEq/L, HCO_3 29 mM/L), and they were still not quite back to normal. *When normal plasma electrolyte pattern was approached, the urine Na concentration rose to a level equal to that of the infused fluid (154 mEq/L), and the sum of urinary Cl + HCO_3 concentration also approximated 154 mEq/L.*
4. During the large NaCl infusion of Experiment 1, the concentration of cations other than sodium and magnesium (total base concentration—sodium concentration fell from 12.2 mEq/L to 4.0 mEq/L.) Plasma potassium determinations showed a fall from 3.9 to 2.2 mEq/L. These results suggest when large volumes are infused, that it is advisable to use a balanced infusion solution of $\text{NaCl} + \text{KCl} + \text{CaCl}_2 + \text{MgCl}_2$ instead of simple NaCl solution.

An unexpected point of interest is the apparent difference in the plasma thresholds for excretion of chloride and sodium in dogs that are passing from normal hydration to dehydration, compared with dogs that are passing in the opposite direction, from the dehydration (caused by loss of gastric juice) to normal hydration by saline therapy. In the normal dogs, we have seen a 24-hour fastnig period cause almost complete suppression of Na and Cl excretion, although the plasma Cl was still at the normal level of 110-115 mEq/L, and $\text{Cl} + \text{HCO}_3$ at 140. When hypochloremic dehydrated dogs were infused with NaCl, however, chloride excretion started by the time the plasma chloride had reached 80 mEq/L, and plasma $\text{Cl} + \text{HCO}_3$ was not over 120 mEq/L (Experiment 1). The kidneys in the salt depleted dogs had apparently lowered their chloride threshold and, when the chloride depletion was in process of correction by saline infusion, the kidneys began to excrete salt much before the normal plasma level was regained. A diagnostic corollary appears

to be, that when a condition of salt depletion is being established, drop of chloride excretion to a low rate is a more sensitive indicator of the condition than is the plasma chloride concentration. But when the condition of depletion of the type caused by loss of gastric juice is in process of correction by NaCl administration, restoration of normal plasma chloride concentration shows more accurately than resumption of chloride excretion when enough saline has been given to correct the condition.

SUMMARY

The condition of dehydration, hypochloremia and alkalosis, observed after severe loss of gastric juice by vomiting or gastric suction, has been reproduced in dogs by the total gastric pouch method of Dragstedt and by gastrotomy with pyloric ligation.

Despite the alkalosis (excess plasma bicarbonate) the urine was acid (pH 5 to 6.4). The acidity of the urine is attributed to the fact that the body deficiency of sodium salts is so great that excretion of both NaCl and NaHCO_3 is almost completely stopped, in the apparent effort to preserve what is left of the body's store of sodium salts. In the absence of bicarbonate in the urine, the pH falls towards that of a solution of free H_2CO_3 .

Sodium chloride infusions corrected the alkalosis and dehydration, replaced the lost plasma sodium and chloride, and permitted excretion of the excess NaHCO_3 , which raised the urine pH to 7.5-8.0.

During saline infusion resumption of chloride excretion was not a safe sign of adequate replacement; replacement was adequate only when plasma chloride concentration was restored to a normal level.

Massive infusion of a solution of NaCl plus glucose was observed to decrease the plasma potassium to less than half the normal concentration, and, by indirect estimation, also the calcium. These effects indicate the desirability of using a balanced electrolyte solution of Na, K, Ca, and Mg when large infusions are given.

Sodium bicarbonate infusion did not correct the plasma electrolyte pattern, raised urinary pH above the physiologic range (pH 8), and caused tetanic convulsions.

The results indicate the possible dangers of using sodium bicarbonate to alkalinize the urine of patients suffering gastric fluid loss, the advisability of using NaCl infusions, and the desirability of guiding the therapy by plasma analyses including at least chloride and CO_2 determinations.

We wish to express our appreciation to Dr. Ole Malm and to Dr. Howard Eder for determining the plasma total base, sodium, and potassium concentration in experiments 1 and 3, and to Dr. D. D. Van Slyke for his great help in analyzing and discussing the data presented.

BIBLIOGRAPHY

- ¹ Gamble, J. L. and M. A. McIver: The Acid Base Composition of Gastric Secretions. *J. Exper. Med.*, **48**, 837, 1928.

- ² Gamble, J. L. and S. G. Ross: The Factors in the Dehydration Following Pyloric Obstruction. *J. Clin. Investigation*, **1**, 403, 1924-25.
- ³ Gamble, J. L.: Carbonic Acid and Bicarbonate in the Urine. *J. Biol. Chem.*, **51**, 295, 1922.
- ⁴ Sendroy, J., S. Seelig, and D. D. Van Slyke: Studies of Acidosis. XXIII. The CO₂ Tension and Acid-Base Balance of Human Urine. *J. Biol. Chem.*, **106**, 479, 1934.
- ⁵ Haden, R., and T. G. Orr: Chemical Changes in the Blood of the Dog After Intestinal Obstruction. *J. Exper. Med.*, **37**, 365, 1923.
- ⁶ Hartmann, A. F. and F. S. Smythe: Chemical Changes in the Body Occurring as a Result of Vomiting. *Am. J. Dis. Child.*, **32**, 1, 1926.
- ⁷ McCance, R. A. and E. M. Widdowson: The Response of the Kidney to an Alkalosis During Salt Deficiency. *Proc. Roy. Soc. London*, **120**, 228, 1936.
- ⁸ Dragstedt, L. R.: Vagotomy for Gastroduodenal Ulcer. *Ann. Surg.*, **122**, 973, 1945.
- ⁹ Van Slyke, D. D. and J. M. Neill: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. I., *J. Biol. Chem.*, **61**, 523, 1924.
- ¹⁰ Van Slyke, D. D. and A. Hiller: Application of Sendroy's Iodometric Chloride Titration to Protein-Containing Fluids. *J. Biol. Chem.*, **167**, 107, 1947.
- ¹¹ Instruction Manual, Flame Photometer, Model 18, The Perkin-Elmer Corporation, Glenbrook, Conn.
- ¹² Adair, G. S. and A. B. Keys: A Micro Method for the Determination of Base by Electrodialysis. *J. Physiol.*, **81**, 162, 1934.
- ¹³ Phillips, R. A., et al.: Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma. Josiah Macy, Jr., Foundation, 565 Park Avenue, New York 21, N. Y.
- ¹⁴ Van Slyke, D. D., A. B. Hastings, A. Hiller, and J. Sendroy, Jr.: Studies of Gas and Electrolyte Equilibria in Blood. XIV. The Amount of Alkali Bound by Serum Albumin and Globulin. *J. Biol. Chem.*, **79**, 769, 1928.
- ¹⁵ Elkinton, J. R. and A. W. Winkler: Transfers of Intracellular Potassium in Experimental Dehydration. *J. Clin. Invest.*, **23**, 93, 1944.
- ¹⁶ Flock, E., J. L. Bollman, F. C. Mann, and E. C. Kendall: The Effect of the Intravenous Injection of Glucose and Other Substances on the Concentration of Potassium in the Serum of the Dog. *J. Biol. Chem.*, **125**, 57, 1938.
- ¹⁷ Holler, J. W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis. *J. Am. Med. Assoc.*, **131**, 1186, 1946.
- ¹⁸ Martin, H. E. and M. Wertman: Serum Potassium, Magnesium and Calcium Levels in Diabetic Acidosis. *J. Clin. Invest.*, **26**, 217, 1947.
- ¹⁹ Fenn, W. O.: The Deposition of Potassium and Phosphate with Glycogen in Rat Livers. *J. Biol. Chem.*, **128**, 297, 1939.
- ²⁰ Pitts, R. F. and W. D. Lotspeich: Bicarbonate and the Renal Regulation of Acid-Base Balance. *Am. J. Physiol.*, **147**, 138, 1946.

ESSENTIAL THERAPEUTIC ADJUVANTS IN THE SURGICAL ARREST OF WOLFF-ISRAEL ACTINOMYCOSIS*†

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THE CLINICAL MANAGEMENT of extensive actinomycotic infections has been considerably advanced by potent antibacterial therapy and an improved understanding of the metabolic requirements of the depleted patient.¹ Therapy with sulfonamides or penicillin has largely replaced treatment with X-ray and such drugs as iodides or thymol. Attention has been directed to a high dietary intake of protein and calories. Even so, it has become increasingly apparent that no form of therapy can substitute for the surgical drainage of pus or excision of tissue devitalized by infection. As attempts at surgical eradication of the disease have become more radical, we have been impressed with the poor tolerance for blood loss and surgical trauma encountered in these chronically ill patients. Further, wound healing has been delayed or faulty, convalescence has been prolonged and some patients have shown incomplete arrest of the disease.

The depletion of reservoirs of body protein seen so frequently in patients with chronic infection is especially common in the patient with advanced Wolff-Israel actinomycosis. Profound anemia and significant weight loss are clinical features of the disease with visceral involvement. Several such patients presented themselves for treatment during a period when we were engaged in a study of the hemoglobin deficiency in chronic shock and the problems of reduced blood volume in the chronically ill patient. Observations of the quantity of blood necessary to overcome the anemia in patients with actinomycosis revealed an unexpectedly great deficit in the total circulating mass of red blood cells. The improved tolerance for surgical blood loss and the acceleration of wound healing noted after blood volume restoration were especially striking. Weight gain and convalescence were rapid in those patients with an adequate dietary intake.

CLINICAL OBSERVATIONS

Five bacteriologically proven cases of Wolff-Israel actinomycosis provide the source material for this discussion. All presented extensive involvement persistent over a considerable period of time. The essential clinical data are summarized in Table I. Although seriously ill, no patient required emergency measures at the time of admission. There was ample opportunity for thorough study and evaluation of the patient anticipatory to election of a surgical program of treatment.

* Read before the American Surgical Association, March 26, 1947, Hot Springs, Va.

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WOLFF-ISRAEL ACTINOMYCOSIS

Secondary anemia and deficiency of body weight were characteristic features of this chronic disease. The deficit in hemoglobin was frequently more apparent on clinical examination than from laboratory estimations of the hemoglobin concentration or hematocrit percentage. The quantity of blood necessary to restore the hematocrit to the range of normal was also in excess of that predictable on the basis of the initial hematocrit value. The deficiency in body weight was made especially prominent by the increase recorded during convalescence. (See Table II).

TABLE I

SUMMARY OF PERTINENT CLINICAL DATA IN FIVE CASES OF PROVEN WOLFF-ISRAEL ACTINOMYCOSIS. ALL RECEIVED BLOOD TRANSFUSIONS, CHEMOTHERAPY WITH PENICILLIN AND HIGH PROTEIN-HIGH CALORIC DIET

Patient	Race	Sex	Age	Site	Duration	Surgery	Result
1: G.H.	W	F	20	Cervico-fascial	2½ yrs.	0	Arrested
2: G.T.	W	F	45	Pleuro-pulmonary-mammary	1½ yrs.	+	Arrested
3: M.M.	W	M	34	Pleuro-pulmonary-cutaneous	6 mos.	+	Arrested
4: E.W.	C	M	43	Abdomino-cutaneous	10 mos.	0	Recurred 13 mos.
5: O.P.	W	M	73	Mandibulo-facial	8 mos.	+	Arrested

TABLE II

COMPOSITE TABLE OF INITIAL AND FINAL HEMATOCRIT VALUES IN RELATION TO TOTAL QUANTITY OF BLOOD GIVEN AS TRANSFUSIONS. ALL PATIENTS ABLE TO EAT SHOWED SIGNIFICANT GAIN IN BODY WEIGHT

Patient	Initial Hematocrit	Blood Given	Final Hematocrit	Weight Gain
1: G.H.	34	3500 cc.	44	24 kilos
2: G.T.	34	7000 cc.	38	7 kilos
3: M.M.	36	2000 cc.	50	9 kilos
4: E.W.	28	3500 cc.	40	18 kilos
5: O.P.	26	3500 cc.	46	-9 kilos*

* Patient O.P. was temporarily unable to eat following resection of one ramus of the mandible.

The true deficiency of circulating red blood cells was more accurately revealed by blood volume determinations than by any other available method. These measurements were performed by the plasma-dye-hematocrit method and standard values were calculated on the basis of the patient's usual weight in health. The results confirmed the existence of "chronic shock," the reduced blood volume associated with weight loss (Lyons *et al*).² The characteristic findings in our cases are illustrated in the record of patient No. 2 (G. T.) as presented in Table III. It is significant that the transfusion of 7,000 cc. of whole blood during the period of hospitalization failed to provide total correction of the estimated deficiency at any time.

In the clinical management of these patients we have been especially interested in four features of the response to therapy: correction of anemia, tolerance for surgical blood loss, wound healing and gain in body weight. With the one exception noted below, all patients were able to accept and retain a high caloric, high protein diet.

Patient No. 1 (G. H., O. C. No. 19053) had been continuously ill for two and one-half years. Recurrent and persistent sinuses in the postero-lateral portions of the neck were communicant with an abscess of the prevertebral

TABLE III
Patient No. 2: G.T.

SUMMARY OF BLOOD VOLUME CHANGES DURING PERIOD OF SURGICAL MANAGEMENT AND CONVALESCENCE. A TOTAL OF 7000 CC. OF BLOOD WAS GIVEN FROM MAY 2-JUNE 22 WITHOUT EVIDENCE OF OVERLOADING THE VASCULAR RESERVOIR

Date	Remarks	Total Cell Mass	Blood Volume	Body Weight
May 2	On admission	1500 cc.	4100 cc.	71.7 kilos
May 7	After 2000 cc. blood and thoracotomy	2400 cc.	4900 cc.	70.8 kilos
May 20	After acute sulfadiazine anemia and 2500 cc. blood	2100 cc.	4600 cc.	69.4 kilos
June 22	After two more operations and 2500 cc. blood. Healed	2200 cc.	5500 cc.	70.3 kilos
July 20	One month after discharge	2000 cc.	5100 cc.	72.6 kilos
Nov. 5	Working	1900 cc.	5000 cc.	78.5 kilos
	Standard for usual weight of 72.7 kilos	2900 cc.	6100 cc.

Actinomyces of Prevertebral Fascial Plane with Cervical Sinuses

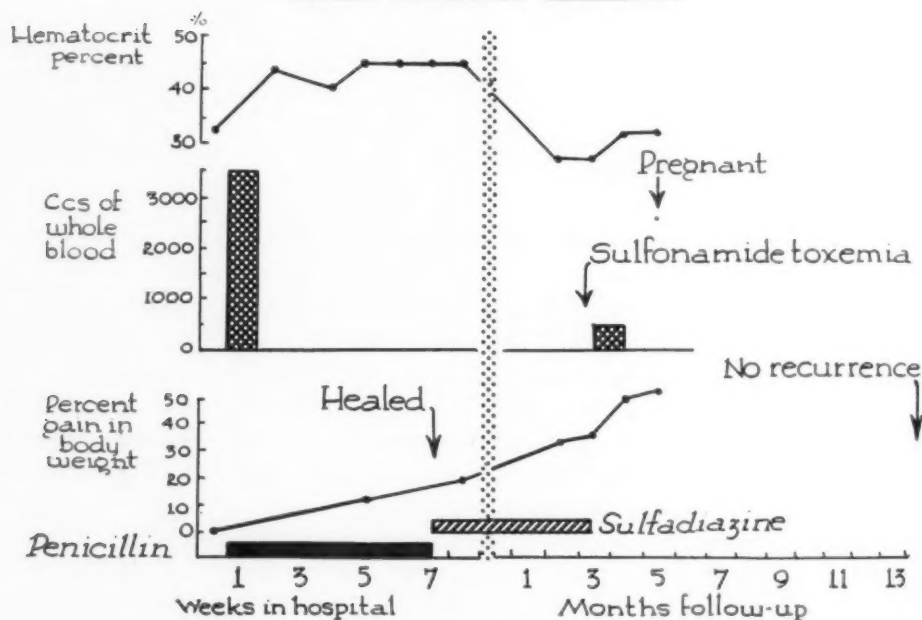


FIG. 1

fascial plane. Destruction of the anterior surfaces of the vertebral bodies was noted on X-ray. Repeated periods of hospitalization for penicillin therapy had failed to arrest the disease and prolonged sulfonamide therapy had been

similarly ineffectual. This same program of therapy was reinstituted after transfusion of 3,500 cc. of whole blood and restoration of the total circulating cell mass to standard value. Wound healing and gain in body weight were noted promptly as shown in Figure 1. It has seemed reasonable to conclude that the therapeutic correction of blood protein deficits by transfusion of whole blood was a measure of critical importance in this patient.

Patient No. 2 (G. T., O. C. No. 46009) developed pulmonary actinomycosis one and one-half years prior to study. Chest wall and mammary extension were later features of the disease. At the time of admission to the hospital

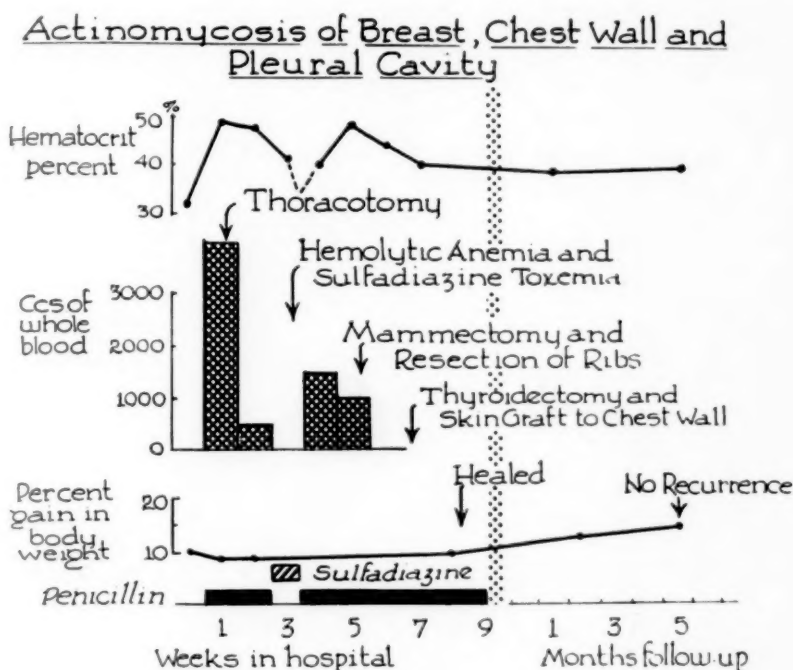


FIG. 2

there were multiple sinuses and a major empyema. Extensive surgical procedures were necessary in stages to provide (1) drainage of pus, (2) excision of tissue devitalized by infection, and (3) skin coverage of chest wall defects. The blood loss incident to these operations was considerable. As has been noted in Table III, complete replacement of the total circulating red blood cell mass was never achieved. The tolerance for surgical blood loss and the rapidity of wound healing were clinically satisfactory. (See Chart II). However, weight gain was a delayed feature noted in later convalescence.

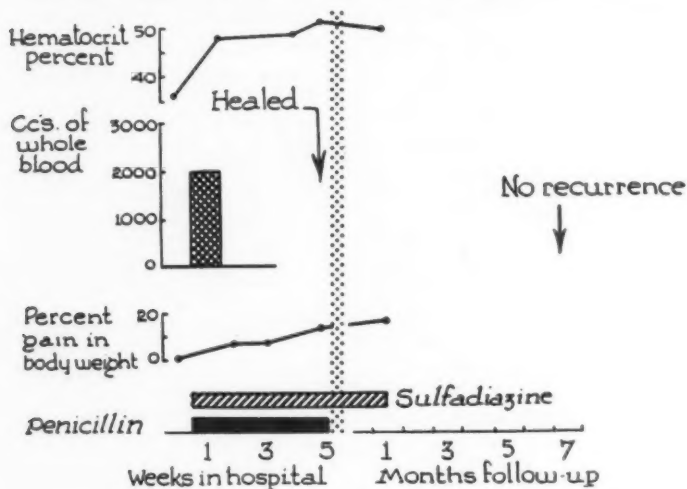
Pleuro-Pulmonary-Cutaneous Actinomycosis

FIG. 3

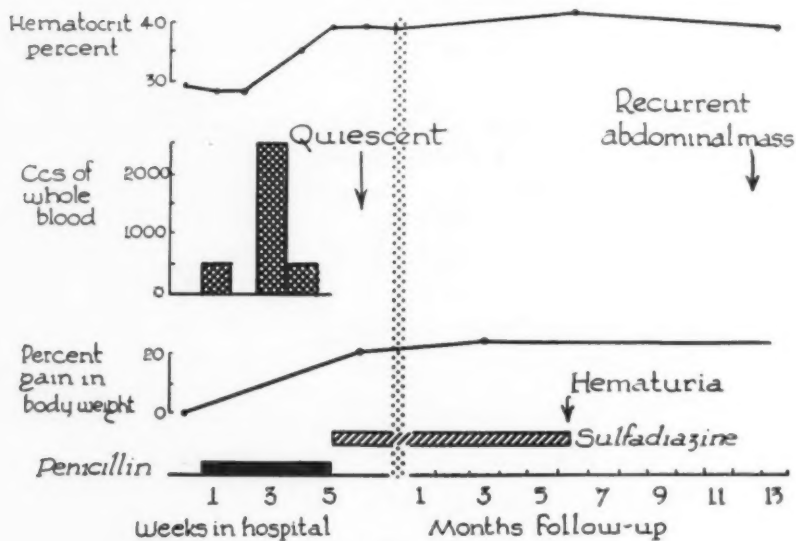
Abdominal Actinomycosis

FIG. 4

Patient No. 3 (M. M., O. C. No. 44978) was referred for diagnosis and treatment of bilateral pleural and pericardial effusions of six months' duration. Shortly after admission an inflammatory mass appeared in the anterior axillary line in the eighth interspace. Incision of this tumefaction established the presence of Wolff-Israel organisms. Shortly thereafter, a similar swelling appeared on the opposite chest wall. Effective therapy consisted of pleural aspirations, transfusion correction of the anemia, penicillin therapy and high protein diet. (See Figure 3).

Patient No. 4 (E. W., C. H. No. T-45-172215) was admitted in May, 1945, for treatment of an abdominal mass and fistula in the right lower quadrant following drainage of an abscess. Rectal fistulas were also present. For a period of seven months he received sulfonamide or penicillin therapy nearly continuously with only moderate improvement. In November, 1945, he was readmitted with recurrent pain and fever. The only new therapeutic procedure introduced at this time was the correction of anemia by transfusion of 3,000 cc. of blood. Within one month, the patient was healed and free of symptoms for the first time (See Fig. 4). The recurrence noted after 13 months' arrest of the disease suggests to us that surgical excision of the lesion should have been done during the period of maximum recovery.

Patient No. 5 (O. P., O. C. No. 42873) was admitted with classical actinomycosis of the face with involvement of the mandible. Correction of anemia by transfusion restoration of the blood volume enabled this frail and elderly (aged 73 years) man to undergo the necessarily extensive excision of diseased tissue with resection of the mandible. Postoperatively an adequate oral intake was temporarily impossible and weight loss was noted. Wound healing, however, was uneventful.

The general efficacy of the program of management adopted is apparent from Table IV. In all of these seriously ill patients, wound healing and significant arrest of the disease were accomplished within four to seven weeks of hospitalization.

It is apparent in Figures 1-5 that penicillin has been adopted as the antibacterial agent of choice during the period of hospital management. In adequate dosage of 25,000-50,000 units every two to three hours, it has proven fully effective against the actinomycetes and relatively free of toxic reactions. Sulfonamides have been reserved for prolonged therapy in patients with surgically inaccessible disease after convalescence has become established. Rejection of sulfonamides as the chemotherapeutic agent of choice for initial therapy has been necessitated by many considerations. The incidence of toxic or urinary tract complications attributable to sulfonamides has made them undesirable during a period of complicated surgical management. Further, these drugs are contraindicated in depleted persons because of the known depressant effect upon hematopoiesis, the intestinal synthesis of essential metabolites, and the appetite in general. Even when used during established convalescence, the sulfonamides are frequently impractical. (See Table V).

DISCUSSION

At the present time, the management of serious actinomycotic infections has emphasized (1) antibacterial therapy, (2) high dietary intake of protein with adequate calories, and (3) drainage of pus and surgical excision of tissue devitalized by infection. As an essential feature of this program, we wish to add transfusion of whole blood in quantities sufficient to restore the total circulating red blood cell mass to or slightly below the standard for the patient's standard or usual weight in health.

TABLE IV
TABLE SHOWING PERIOD OF HOSPITALIZATION NECESSARY FOR CLINICAL ARREST OF THE DISEASE AND WOUND HEALING

Patient	Pre-Operative Hospital Stay	Number of Operations	Total Hospital Stay
1: G.H.....	0	42 days
2: G.T.....	5 days	3	46 days
3: M.M.....	1	27 days
4: E.W.....	0	49 days
5: O.P.....	8 days	1	31 days

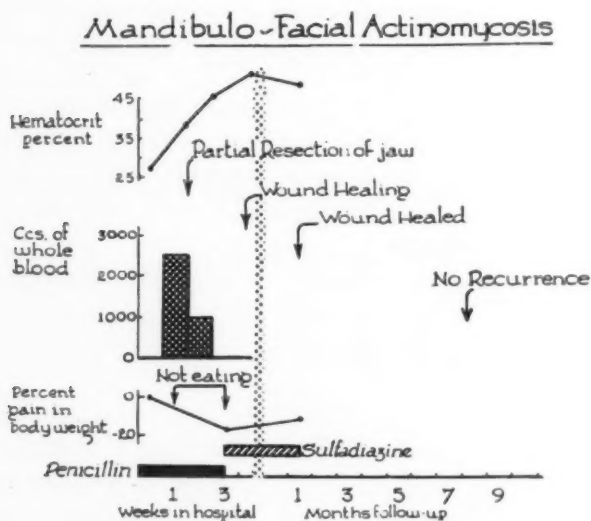


FIG. 5

Most surgeons will concede considerable blood loss in the excision of the inflammatory mass typically associated with Wolff-Israel actinomycosis. We have become especially aware of this factor and believe that transfusions of whole blood before and during surgical operations provide the only available method of improving tolerance for surgical blood loss.

Anemia is a prominent feature of actinomycotic infections. A fundamental defect in hemoglobin metabolism in patients with chronic infections has been elucidated by Wintrobe *et al.*³ Whipple and his co-workers⁴ have emphasized

the prior demand of needed hemoglobin upon newly available dietary protein. These basic facts suggest that antibacterial therapy, transfusion of blood and drainage of pus constitute initial therapy in chronic infections.

Within Schoenheimer's⁵ concept of "dynamic equilibrium," Whipple and associates⁶ have elaborated the thesis of a "metabolic pool" of "labile protein reserves." The chief reserves of protein are in the tissue cells. In simple malnutrition with anemia, the demand for blood proteins will further deplete the already diminished reserves of tissue protein unless the dietary intake of food protein be abundant.⁷ In chronic sepsis with nutritional depletion and anemia, this phase of protein metabolism is complicated by the inability to produce new

TABLE V

SUMMARY OF DRUG THERAPY AS ADMINISTERED DURING AND AFTER HOSPITALIZATION. IN THREE OF THE FIVE PATIENTS A TOXIC REACTION WAS NOTED IN CONSEQUENCE OF SULFONAMIDE THERAPY. A MILD ANEMIA WAS CHARACTERISTIC OF PROLONGED SULFONAMIDE THERAPY

Patient	Days of Penicillin Therapy	Days of Sulfadiazine Therapy	Sulfonamide Toxemia
1: G.H.....	39 days	96 days	+
2: G.T.....	42 days	4 days	+
3: M.M.....	14 days	27 days	0
4: E.W.....	36 days	169 days	+
5: O.P.....	20 days	82 days	0

hemoglobin and new red blood cells. The only satisfactory method of correcting the anemia in chronic infections is the transfusion of whole blood in amounts adequate to restore the total circulating red blood cell mass to standard values. This permits utilization of protein reserves primarily for wound healing.

Our observations suggest that after correction of anemia the wounds heal even though tissue protein reserves are not replaced immediately. Adequate wound healing has been noted in patients without concomitant weight gain. Apparently, the synthesis of new protein assigns priority to wound healing rather than to replenishment of tissue protein reservoirs. Restoration of tissue protein depends upon the intake of food protein and calories in excess of normal requirements. The most important and reliable evidence of this replacement is progressive and sustained weight gain. Thus, blood transfusion and adequate protein intake are both essential features of the supportive nutritional program in the surgical arrest of the disease.

CONCLUSIONS

1. Depletion of blood proteins is a significant feature of the malnutrition observed in patients with Wolff-Israel actinomycosis.
2. Precise evaluation of the anemia and hypoproteinemia demands repeated blood volume determinations throughout the period of clinical management.
3. Transfusion of whole blood in quantity sufficient to restore the total

circulating red blood cell mass is obligatory in the pre-operative preparation of the patient.

4. Replacement of blood lost during surgical operations demands whole blood transfusions to maintain the pre-operative status.

5. Postoperatively, maintenance of the blood proteins is necessary to divert labile protein reserves to the purposes of wound healing.

6. Replenishment of tissue protein reserves, as evidenced by weight gain, demands an intake of food proteins and calories in excess of normal requirements.

7. Penicillin is the antibacterial agent of choice during the period of hospitalization and initial surgical management. Sulfonamides (sulfadiazine) are reserved for prolonged medication during convalescence.

8. The surgical procedures recommended in the treatment of actinomycosis are:

- (a) Drainage of abscesses.
- (b) Excision of accessible foci of devitalized and infected tissue.
- (c) Reparative closure of resultant tissue defects by secondary suture, sliding or pedicle flaps and free skin grafts.

9. Under this program of management the disease has been promptly arrested, wounds have healed and body weight has been restored.

REFERENCES

- ¹ Kolouch, F., and L. F. Peltier: Actinomycosis, *Surgery* **20**, 401-430, 1946.
- ² Lyons, C., H. S. Mayerson, J. H. Clark, W. Nelson, and P. T. DeCamp: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient. I. Concept of Chronic Shock. (In Press, *ANNALS OF SURGERY*.)
- ³ (a) Cartwright, G. E., M. A. Lauritsen, P. J. Jones, I. M. Merrill, and M. M. Wintrobe: The Anemia of Infection. I. Hypoferremia, Hypercupremia, and Alterations in Porphyrin Metabolism in Patients. *J. Clin. Investigation* **25**, 65-80, 1946.
(b) Cartwright, G. E., M. A. Lauritsen, S. Humphreys, P. J. Jones, I. M. Merrill, and M. M. Wintrobe: The Anemia of Infection. II. The Experimental Production of Hypoferremia and Anemia in Dogs. *J. Clin. Investigation* **25**, 81-86, 1946.
- ⁴ Robscheit-Robbins, F. S., L. L. Miller, and G. H. Whipple: Hemoglobin and Plasma Protein; Simultaneous Production During Continued Bleeding as Influenced by Amino Acids, Plasma, Hemoglobin, and Digest of Serum, Hemoglobin, and Casein, *J. Exper. Med.* **77**, 375-396, 1943.
- ⁵ Schoenheimer, R.: *The Dynamic State of Body Constituents*, Cambridge, Mass., Harvard University Press, 1942.
- ⁶ Whipple, G. H., and S. C. Madden: Hemoglobin Plasma Protein and Cell Protein—Their Interchange and Construction in Emergencies. *Medicine* **23**, 215-224, 1944.
- ⁷ Miller, L. L., F. S. Robscheit-Robbins, and G. H. Whipple: Anemia and Hypoproteinemia. *J. Exper. Med.* **85**, 267-275, 1947.

DISCUSSION.—DR. RUDOLPH MATAS, New Orleans: I want to congratulate Doctor Gage and Associates on their success in improving the prognosis of actinomycosis. The results of chemo-therapy with the sulfonamides is disappointing as must be expected in resorting to drugs so unfit for prolonged administration, especially in the chronic visceral lesions that are so inaccessible to surgery. The combination of penicillin with massive whole blood transfusion and high dietary intake of protein, is a decidedly valuable contribu-

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tion in which the advances in therapeutic hematology may justly claim even a greater share of credit for the result than surgery with or without the aid of antibiotics. The old recognized value of potassium iodide should not be overlooked in the excitement of the new therapy.

DR. ALTON OCHSNER, New Orleans: Doctor Gage's presentation is more significant than would appear at first thought, not only because of the results he has obtained in the treatment of actinomycosis, a disease which in its extensive form has defied treatment, but also because of the results obtained in other chronically ill patients. Dr. Champ Lyons for the past two years has been carrying on extensive investigations on our service at Tulane and has found that the chronically ill patients suffering from chronic infection, specific and non-specific, and suffering from neoplasms have alterations in their blood volume which are not detected by the ordinary laboratory examination. Although many of these patients appear to have no anemia because of the relatively normal hemoglobin per cent value and relatively normal red cell per cu. mm. value, they actually have severe anemia because of a contracted blood volume. One must know the total circulating hemoglobin and the total circulating red cell mass to treat these chronically ill patients satisfactorily. This can be ascertained only by the determination of the blood volume.

Dr. George Whipple has shown that there is a preferential demand on protein for the synthesis of hemoglobin, and in the individual who has a deficient amount of hemoglobin, the protein taken in may be utilized entirely for the synthesis of hemoglobin and may not be available for repair of tissues. This is particularly important in the chronically ill patient, such as the one with actinomycosis.

For some time we have known empirically that the chronically ill patient required blood preoperatively, because we knew that unless they received blood before operation, they could not withstand a major surgical procedure without getting into difficulty. Without knowing what their actual deficiency was, we were at a loss to know what to give them. By the determination of the blood volume we can estimate what their actual deficiency is and correct this by the administration of adequate amounts of whole blood. During the past two years we have found that in our chest patients an average of 2.5 liters of blood was required preoperatively to replenish their deficiency.

The anemia associated with actinomycosis is especially important because if sulfonamides are used therapeutically the anemia is likely to be aggravated. It is because of this, as emphasized by Doctor Gage, that the chemotherapeutic management early in the course of the disease should consist of the administration of penicillin rather than sulfonamides. Later, after the anemia has been corrected and after repair of the tissue has begun, sulfonamides can be started and must be continued for a long period of time, usually for many months. With the institution of the regimen outlined by Doctor Gage and his associates, we have been able to control and to bring about a cure in cases of actinomycosis which previously would not respond to any type of therapy. Although my remarks have been concerned principally with the anemias and chemotherapy, I would not want to leave the impression that surgical therapy is not equally as important in these cases.

DR. I. S. RAVDIN, Philadelphia: Doctor Gage is to be congratulated on this presentation. In his paper yesterday, Doctor Zintel pointed out a similar mechanism in the treatment of patients with carcinoma of the colon. It has universal application in patients who have a hemoglobin deficiency, and at the same time a deficiency in the reserve stores of protein. Regardless of the type of feeding, the protein and minerals will go to restoring hemoglobin, and not toward replenishment of the protein stores. I think attention should be called to the work of Paul Cannon on the control of infection under such circumstances. He has pointed out that as soon as a protein deficiency exists in the experimental animal, antibody formation and phagocyte formation is retarded. Thus, two of the biologic factors which have to do with control of infection are disturbed.

In speaking of diet under the circumstances described by Doctor Gage, one should

remember that though it is important to give adequate protein, if large amounts of carbohydrate and protein are fed, the fat content of the diet can be increased, then you can prevent large losses of protein in the urine. Where liver protection is not so important, the restriction of fat is not so important.

DR. MIMS GAGE, New Orleans (closing): In answer to Doctor Churchill's question, I would state that we use the plasma dye technic to determine the blood volume. The technic may be criticized as to its accuracy. However, we believe that it is sufficiently accurate to demonstrate and call our attention to the presence of chronic shock in the chronically ill or debilitated patient. By the use of plasma dye method in estimating the blood volume preoperatively, we have been able to demonstrate the presence of chronic shock, overcome this state of chronic shock, return the patient to a normal physiologic basal line, making it possible to proceed with major surgical procedures with most gratifying postoperative convalescent and clinical curves. I am convinced that by determining the blood volume in the chronically ill patient and restoring the patient to physiologic balance we have saved many lives which would have been lost without the above knowledge.

AN EVALUATION OF METHODS OF PENICILLIN THERAPY IN THORACIC SURGERY*†

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PENICILLIN is now being widely used in the active treatment of or prevention of infection in many medical and surgical conditions. Various methods of administration have been recommended and are now being used, whereas the final decision as to which are best or preferable have not been made. The ideal method may vary according to the condition under treatment. It was thought worthwhile to determine concentrations of penicillin in blood serum and pleural fluid following technics of administration commonly employed, and to consider their relative merits. This study was made on humans and on dogs having intrathoracic operations in which a lung lobe or an entire lung was resected.

It is believed by the authors that the study of penicillin titers in appropriate body fluids affords a somewhat more controlled means of evaluating relative therapeutic efficacy of a given method of administration than is possible by clinical observation in a comparable number of patients. Without large numbers of patients, affording statistical proof of the superiority of a given technic by its therapeutic response, clinical observation may be misleading.

In Vitro studies by Rammelkamp and Keefer¹ indicate that penicillin has a bactericidal effect on hemolytic streptococci in serum in concentrations of as little as 0.015 Florey units per cc. They state that a concentration between 0.03 and 0.3 units per cc. of whole blood was necessary for maximal killing of the hemolytic streptococcus.

Staphylococcus aureus was found in general to be more resistant to the drug, requiring about 0.15 units per cc. of penicillin for maximum killing effect. Growth of organisms is inhibited at considerably lower concentration. They noted that as the blood titer of penicillin falls following intramuscular administration, the bactericidal action tends to be maintained, and that there was an anti-staphylococcic action of the whole blood for almost an hour after the serum concentration of penicillin was too low to detect.

Different strains of staphylococci exhibit wide variations of susceptibility to penicillin, sensitivity ranging from 0.02 units per cc. to 0.35 units per cc. for bactericidal effect of 29 strains tested in veal infusion broth.

Other organisms display a wide range of susceptibility to penicillin, and dosage and technic of administration should be regulated accordingly.²

* Read before the American Surgical Association, March 26, 1947, Hot Springs, Va.

† This work was done in part under a grant from the Etta Baker Fund for Tuberculosis Research.

METHODS

Intramuscular, intratracheal, aerosol, and intrapleural administrations of penicillin were studied with assays made on serum, and in some instances pleural fluid, at given time intervals following administration. Most of the determinations were made from clinical material. Studies on dogs, most of which had undergone pneumonectomy for other experimental purposes, were used to supplement clinical data. A tabulation of the number of experiments performed appears in Table I. In general each experiment represents a single administration of penicillin followed by one to several fluid level determinations made at various intervals.

TABLE I
PENICILLIN THERAPY
Experiments Performed

Method of Administration	Man		Dog	
	Serum	Pleural Fluid	Serum	Pleural Fluid
Intramuscular.....	16	20	4	0
Intratracheal.....	9	0	8	0
Aerosol.....	12	0	10	0
Intrapleural.....	8	20	12	12
Total.....	85		46	

Number of experiments performed on patients and on dogs for each of the techniques of penicillin administration studied.

Assays were made by a modified cup-agar technic as described by Abraham, *et al*³ and by Foster and Woodruff.⁴ A sensitive strain of *Staphylococcus aureus* was used as the test organism. In general, assay values were considered reliable for penicillin concentrations within therapeutic range, i.e., 0.03 units per cc. and higher.

RESULTS

A. Intramuscular Injections.

Serum levels. Serum titers of penicillin following intramuscular injection of 20,000 units are represented in Chart 1. Maximum, average and minimum levels are indicated. Averages, represented by solid lines, are made from four to eight assay determinations for each time interval indicated. It is seen that maximum levels are attained in 15 to 30 minutes after injection. In two hours there is a minimal therapeutic level. This is in general agreement with other investigators in this field.^{5, 6, 7} (Results of animal experiment agree with humans).

Dogs given intramuscular penicillin, in doses proportional to weight corresponding to 20,000 units for a 70 kg. man, showed a similarly shaped serum-level curve for the first one-and-one-half hours, with maximum levels at one-half hour ranging from 0.34 units per cc. to 0.43 units per cc. At the end of one-and-one-half hours, titers ranged from 0.14 unit per cc. to 0.23 unit per cc.

Pleural fluid levels. Pleural fluid penicillin levels obtained following intramuscular administration were extremely variable, depending apparently upon the duration of treatment, manner in which the fluid was obtained, i.e. whether by direct thoracentesis or from a Pezzer catheter or other drainage tube, and perhaps other factors such as the amount of fluid present in the pleural cavity, the presence of infection with penicillinase-forming organisms, and perhaps the condition of the pleural serosa. Table II represents values obtained which are thought to be relatively comparable in the conditions under which they were obtained, i.e. absence of supplementary medication, absence of infection and samples freshly drawn from the pleural cavity.

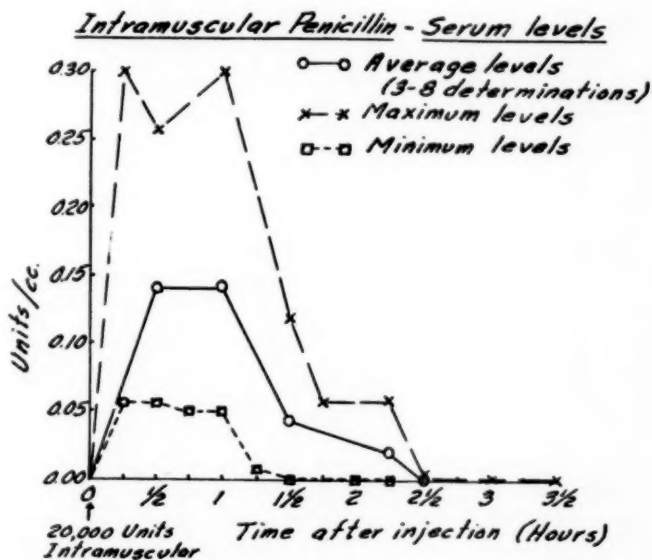


CHART I.—Serum levels (units per cc.) at various time intervals following intramuscular injection of 20,000 units of penicillin.

Pleural fluid penicillin levels are seen to be maintained at therapeutic levels for two hours or longer, reaching a maximum at about one-and-one-half hours after injection. On one occasion a penicillin titer of 0.03 units per cc. was noted six hours after the last intramuscular injection of 20,000 units.

In general it is noted that 40,000 unit doses intramuscularly give more than double the pleural fluid penicillin level rendered by 20,000 unit doses.

Cooke and Goldring⁷ concluded that the concentration of penicillin in edema, ascitic and pleural fluids tend to approximate that of the blood serum. The present study seems to indicate that titers of pleural fluid do not necessarily approximate those of the serum for any particular time after administration but rather fluctuate more gradually and may approximate the median blood serum level over an extended period. It would seem that a large amount

of pleural fluid or thickened pleura would cause more gradual fluctuations in the pleural fluid penicillin level.

B. Intratracheal Instillations.

Intratracheal instillations of penicillin were made on nine patients, usually following bronchoscopy, but on three occasions by use of a Jackson cannula. Results by the two technics were essentially similar, and are combined in their graphic representation in Chart 2.

TABLE II
PENICILLIN THERAPY

Dose	Hours After Administration			
	$\frac{1}{2}$	1	$1\frac{1}{2}$	2
I.M.	u/cc.	u/cc.	u/cc.	u/cc.
40,000 U.....	0.23	0.24	0.15
40,000 U.....27
40,000 U.....	0.06	.18	.28	.28
40,000 U.....	.15
20,000 U.....	.24
20,000 U.....03
20,000 U.....	tr.
20,000 U.....12
20,000 U.....08

Pleural fluid penicillin levels (units per cc.) at various time intervals following intramuscular injection of 40,000 U and 20,000 U doses in man.

Single experiments were performed with 200,000; 100,000 and 90,000 unit doses (20,000 units per cc. in each case). Maximum, minimum and average levels are noted for 50,000 unit doses, average values representing from three to five determinations each.

Maximum levels were uniformly noted after one-half hour, with generally good therapeutic serum penicillin concentrations at that time. By the end of two hours after 50,000 unit doses, minimum therapeutic serum levels were noted, and at three and four hours only traces of the drug were found in the serum. Increased dosage gave correspondingly higher serum levels. The sodium salt was used in these experiments, although calcium penicillin is reported to be more pleasant to take and has less local tissue toxicity.^{8, 9}

Intratracheal penicillin administered by bronchoscope to eight dogs in doses of 20,000 units (equivalent by weight to approximately 100,000 units in the human) yielded average serum penicillin levels.

C. Aerosol Administration.

Considerable technical difficulty was encountered in administering penicillin by aerosol efficiently enough to yield detectable blood levels. Use of a BLB mask through which the nebulized penicillin was inhaled resulted in great loss

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of the drug due to precipitation of particles on the lining of the mask, apparently because of turbulence of flow consequent to poor streamlining. The best results in blood levels, and presumably also in dissemination of the aerosol throughout the lungs, were obtained as follows: The nebulizer* outlet is held in the mouth, the lips forming a seal. An oxygen (or compressed air) flow of four to five liters per minute is used. A Y-tube between the oxygen source and the nebulizer has one arm open, acting as an exhaust when the nebulizer is not being actuated. Pressing the thumb over this exhaust opening forces the oxygen through the nebulizer.⁸ The patient is instructed to breathe as

Intratracheal Penicillin - Serum levels

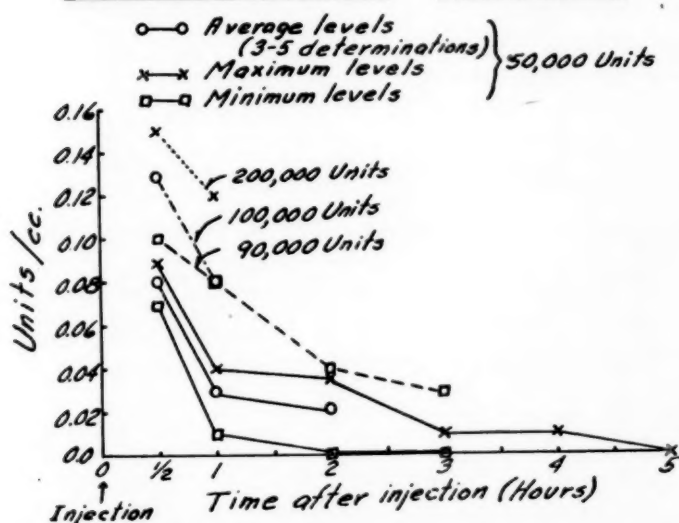


CHART 2.—Serum levels (units per cc.) at various time intervals following intratracheal administration of penicillin in various doses by bronchoscope or Jackson cannula. (Traces of penicillin are indicated on the graph as 0.01 unit per cc.).

slowly and deeply as is comfortable. During the first half of the inhalation phase the nebulizer is actuated by pressing the thumb over the open arm of the Y-tube, and the patient breathes in through his mouth. The inhalation is completed through the nose with the thumb removed from the exhaust outlet. Expiration is through the nose. A co-operative patient can learn the technic quickly. With ordinary breathing aerosol mists can be seen to be exhaled. Using the technic described, no such mists are visible. Barach, *et al*² advocate holding the breath for a moment after inhalation to insure maximum effectiveness. This seems to be less comfortable over an extended period of time than the technique herein described. One or two rinses with one-half to one cubic

* Made by the Vaponephrin Company. The medium mass diameter of the droplets was approximately 2.5 micron.

centimeter of water or saline in the nebulizer carburator are necessary to deliver most of the drug because of the drying and concentration of the solution during nebulization. As much as half the initial dose has on occasion been recovered from the nebulizer after it had been considered that the treatment was completed.

Sodium penicillin was administered in 30,000 unit doses in 1.5 cc. of saline. Administration usually required from one to one-and-one-half hours. None

TABLE III
PENICILLIN THERAPY

Time	Serum Level (U/cc.)
$\frac{1}{2}$ hour.....	0.24
1 hour.....	0.18
$1\frac{1}{2}$ hours.....	0.09
2 hours.....	0.05

Penicillin serum levels in dogs following 20,000 U intratracheally. Each value represents the average of three to eight determinations.

Aerosol Penicillin - Serum levels

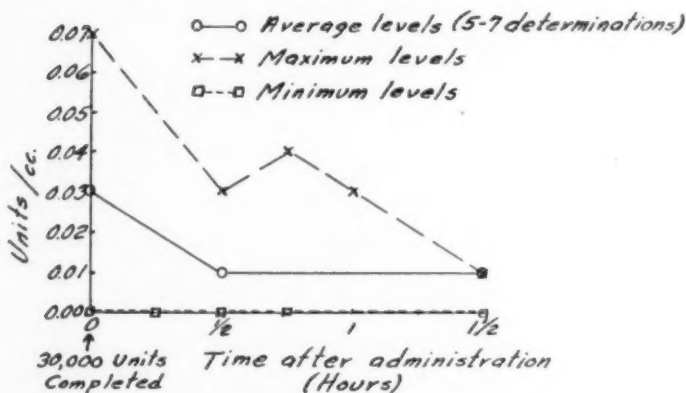


CHART 3.—Blood serum levels (units per cc.) at various time intervals following administration of 30,000 units of penicillin by aerosol.

of the patients complained of the taste, or of irritation of the upper respiratory tract. Blood serum levels appear in Chart 3.

Maximum serum levels were noted at the completion of administration, representing, on the average, only minimal therapeutic levels. From one-half to one-and-one-half hours after nebulization only traces of the drug were usually noted.

Aerosol penicillin was attempted on 10 dogs, usually delivered through a positive pressure anesthesia apparatus. Some of the dogs were normal; others were undergoing pneumonectomy at the time of administration. The usual dose was 16,000 units, corresponding by weight to about 70,000 units in man. With one or two exceptions blood serum titers showed at most a trace of

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penicillin. Synchronizing nebulization with respiration was not attempted, and much was doubtless lost in both exhaled mists and at angular points in the apparatus, disturbing a smooth air flow.

D. Intrapleural Administration.

Serum levels. Penicillin was administered intrapleurally and blood serum assayed for penicillin in eight patients. Assay determinations are represented in Chart 4.

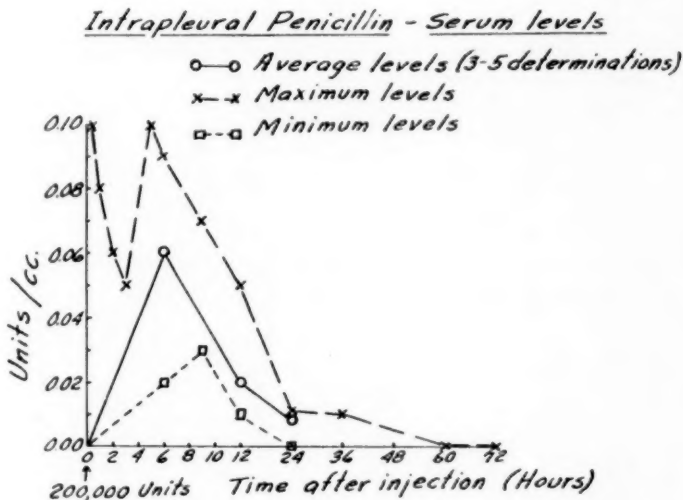


CHART 4.—Blood serum levels (units per cc.) at various time intervals following intrapleural administration of 200,000 units of penicillin.

Administration of the drug was by thoracentesis, or following pneumonectomy it was combined with 500 cc. of plasma instilled into the empty pleural cavity. No appreciable difference in serum penicillin levels were observed from the two technics, and the results are combined. Therapeutic levels were present in the serum for 9 to 12 hours with traces detectable up to 36 hours after injection.

The curve representing maximum penicillin levels was made almost entirely through the first 24 hours from determinations on one patient after a single intrapleural injection. The jump in concentration occurring between the third and fifth hour is unexplainable unless one assumes an increased rate of absorption from the pleural cavity, or a diminished urinary excretion during that time. Certainly a wide range of serum penicillin values through the first 12 hours is noted in the present studies.

The curve of maximum values indicates that absorption of penicillin takes place from the pleural cavity sufficiently rapid to give therapeutic serum levels within the first half hour, rather than at six hours, as is suggested by the average curve.

Pleural fluid levels. Penicillin concentrations in the pleural fluid following intrapleural administration of 200,000 units are represented in Chart 5. Extremely high titers were found immediately after injection, as is to be expected. Average levels were seen to be maintained at good therapeutic values through at least 60 hours, and individual determinations at 84 and 114 hours still showed 0.38 units per cc. and 0.21 units per cc. respectively.

Intrapleural instillation of penicillin was made into the pleural cavities of ten dogs sometime following pneumonectomy and of two dogs at the time of pneumonectomy. The dosage was 50,000 units in 200 cc. of pooled human

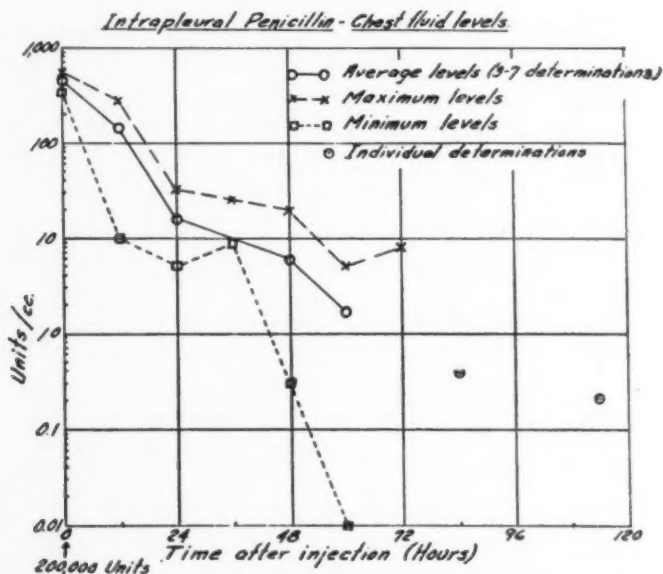


CHART 5.—Penicillin titers (units per cc.) in the chest fluid at various time intervals following intrapleural injection of a 200,000 unit dose.

plasma. Chest fluid and blood serum assays revealed values in no way comparable to those in humans. Serum levels were extremely variable, ranging from 0.03 to 1.5 units per cc. within the first five hours, and from 0.00 to 0.12 units per cc. at about seven hours. At 24 hours no penicillin was detectable in the serum of any of the twelve animals. (Compare with Chart 4). Chest fluid levels were also erratic, ranging from 2.90 to 44.0 units per cc. within the first four hours, and from 0.10 to 1.80 units per cc. at about seven hours. At 24 hours the chest fluid contained no detectable penicillin in any of the 12 dogs. Evidently penicillin is absorbed from the pleural cavity much more rapidly in dogs than in man.

DISCUSSION

The serum levels of penicillin resulting from use of the technics here studied are represented in Chart 6. The curves drawn represent the average values as shown on Charts 1, 2, 3 and 4.

Intramuscular penicillin generally gives the highest serum titers of the methods here studied, and is the most efficient routine method of administration for maintaining adequate serum levels. It has the disadvantage of frequent, rather painful injections, thus unpleasant for the patient and for the nursing staff. Doses larger than 20,000 units, or more frequent administration than once every three hours, would prevent serum concentration from falling to zero between injections and would be indicated for patients not responding well to the more conventional dosage schedule.

Intratracheal penicillin in 50,000 unit doses yields relatively poor and transitory serum levels. It could not ordinarily be used as a routine method of administration because of the technical difficulty involved and the discomfort

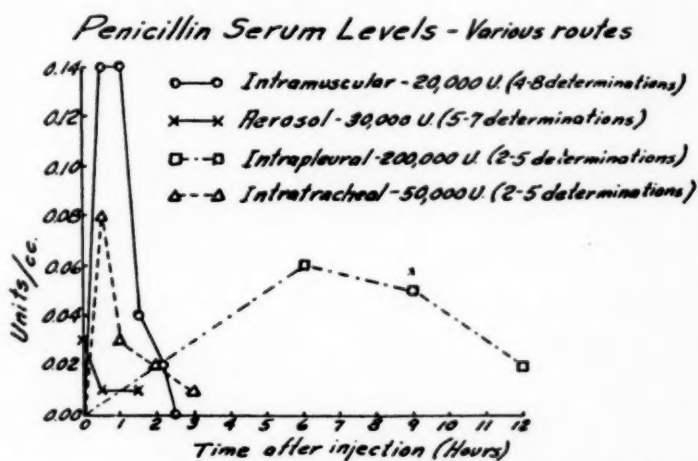


CHART 6.—Penicillin serum levels (units per cc.) at given time intervals following administration by various routes.

to the patient. In patients with chronic bronchitis, asthmatic bronchitis, bronchiectasis or chronic lung abscess it may be of value in its local effect on the disease process. Kay and Meade¹⁰ report intratracheal penicillin to be of particular value in the treatment of chronic bronchitis, minimal bronchiectasis, advanced inoperable bronchiectasis and in preoperative preparation of lobectomy patients. In many of their patients they noted a more rapid and more marked improvement than had been observed by the use of intramuscular administration of 25,000 units every three hours.

Aerosol administration of 30,000 unit doses of penicillin yielded the poorest serum concentrations of all the methods studied. Here again, except for the possible local effect of the drug in diseases of the bronchial tree it would not be indicated as a routine method of therapy. The concomitant oxygen therapy may be indicated for some patient, but unfortunately in these same individuals one could not expect the cooperation or ability necessary for efficient utilization, as is required for the technic described above. A nasal

catheter has too small a diameter to be an efficient conduit for the mists, and a large share of what should reach the respiratory tract would doubtless be exhaled, as was noted with ordinary breathing. The BLB mask is not an efficient medium for aerosol therapy in the limited experience of the authors. Mutch and Rewell¹¹ report high blood titers of penicillin using approximately 200,000 to 300,000 unit doses administered in one-half hour administrations, using a Collison nebulizer and BLB oxygen unit, and running eight to ten liters of oxygen per minute. They report wastage of 60 to 75 per cent of the solution. Barach, *et al*⁸ and Vermilye¹² found relatively low serum concentration of penicillin following aerosol therapy, but they cite case histories in which distinct clinical improvement seemed directly attributable to this method of administration. It would seem wise to avoid considering aerosol penicillin as a panacea for the treatment of chronic infectious diseases of the respiratory tract until more data has been accumulated as regards the blood penicillin levels, to indicate a distinct advantage in this type of therapy. Aerosol is certainly not a substitute for intramuscular injections in conditions in which an adequate serum penicillin level is desired. If it is used indiscriminately in general practice and in the home, where Vermilye implies it should be of great value, it may easily result in great waste of the drug, needless expense and office visits for the patient and a false sense of security in the treatment given.

A clinical study of penicillin used by the aerosol method of administration was carried out by Dr. Erwin Levin of our Medical Department following the completion of the present study. This method of administration was used in 34 patients having bronchiectasis, chronic bronchitis or carcinoma of the lung. In some patients it was used as a means of treating active infection. In others it was used as a means of preparing the patients for operation. The usual dosage was 50,000 units of penicillin in 2 cc. of saline solution administered over a period of 20 minutes. This dosage was repeated every three hours five times a day for one to several weeks. In 21 of the patients all of the gram positive organisms disappeared from the sputum, and in 13 the number of these organisms was markedly diminished. Of the 11 patients prepared for operation by aerosol treatment for three to seven days, only two showed the presence of gram positive organisms in the surgical specimen. In six other patients the gram positive organisms disappeared from the sputum but returned in three to five days after the penicillin was discontinued. Of ten patients with chronic bronchitis treated by this method, nine showed little or no improvement. Doctor Levin's conclusion was that aerosol administration was an effective method for gram positive organisms in the sputum and was useful as a preoperative measure. About 20 per cent of these patients developed a rash or a glossitis or pharyngitis four to seven days after the treatment was begun. The treatment required the co-operation of the patient.

Intrapleural penicillin in 200,000 unit doses gives a sustained serum concentration at therapeutic levels for nine to 12 hours after administration, evidently rising to adequate levels within the first hour rather than over the

first six hours as indicated in Chart 6. Intrapleural injection is limited in its usefulness because its local effect in the pleural cavity is its primary objective, thus its use is limited to patients in whom fluid already exists in the pleural cavity, or following surgery such as pneumonectomy in which prophylaxis against empyema is desired. In several patients it was used concomitantly with intramuscular injections, and isolated serum assay suggests an additive, or even what might be called a symbiotic, effect from the two techniques; i.e., higher penicillin concentrations sustained for longer periods of time than might be expected from a simple summation of titers. There is insufficient data to consider this as more than a suggestion, however.

Pleural fluid penicillin levels following intramuscular injection are generally adequate following 20,000 unit doses, but more efficient use of the drug is apparent with 40,000 unit doses. From the limited data here presented it is evident that intramuscular penicillin, 40,000 units every three hours, would adequately control pleural infection by penicillin-sensitive organisms.

When thoracenteses are indicated for removing excess pleural fluid, where the chest is surgically or otherwise open, or when more resistant infectious organisms are encountered in the pleural cavity, intrapleural administration is preferred because of its great local concentration, absence of frequent painful injections and duration of action.

We have used this method of administration in 18 patients following total pneumonectomy for carcinoma of the lung, and in two patients with pulmonary suppurative disease. The only complication of empyema resulted following one of the two resections for pulmonary suppuration. In this patient a draining sinus was present at the time of pneumonectomy, thus contamination of the pleural cavity was considerable during the operation. This patient did not develop a bronchial fistula. One of the 18 patients with carcinoma of the lung developed a temporary bronchial fistula which healed spontaneously without the production of an empyema. One of the patients died of bronchial pneumonia in the remaining lung, but without a bronchial fistula or empyema on the side of surgery.

Intrapleural injections once every three days should be adequate for maintaining high therapeutic levels. When penicillinase-forming organisms* are present in a mixed infection empyema, therapy should be directed at eliminating these organisms first, otherwise the penicillin may be rapidly inactivated, the resistant organisms may keep the infection active, and there is danger of penicillin resistance developing in the otherwise sensitive organisms due to prolonged exposure to non-bactericidal fluid levels of the drug.¹³

CONCLUSION

Intramuscular injection of penicillin is probably the best of the methods here studied as far as obtaining desirable blood serum levels in the non-surgical patient.

* *E. coli*, *Proteus vulgaris* and other gram negative motile bacilli are often potent penicillinase formers.

Intramuscular injections of 40,000 units of penicillin every three hours maintains good therapeutic levels in the pleural fluid. Twenty thousand unit doses appear much less effective.

Intratracheal instillation of 50,000 units of penicillin gives therapeutic serum titers at one-half hour but falls to minimum therapeutic levels by one hour. Doses of 100,000 units and 200,000 units give correspondingly higher serum values within the first hour after administration.

Aerosol penicillin in a dose of 30,000 units yields generally poor, but sometimes therapeutically adequate serum levels for as much as an hour after completion of administration. Larger doses would probably produce somewhat higher values. This technic is not to be regarded as a substitute for more established forms of administration in routine use, and until more efficient technics of utilization are developed and proved, aerosol penicillin should not be regarded as a home or office panacea.

Penicillin injected intrapleurally in 20,000 unit doses maintains therapeutically adequate serum levels for nine to 12 hours. Pleural fluid levels remain high for as much as four or five days after administration by this method.

SUMMARY

Several technics of penicillin therapy were studied, using serum and pleural fluid drug concentrations as primary criteria for evaluating the relative efficacy of treatment in thoracic surgical diseases.

(We are indebted to Mrs. Virginia Green, PhB., for the organization of the bacteriologic work and to Miss Mary Augustine, B.S., for the penicillin assay determinations.)

REFERENCES

- ¹ Kammelkamp, C. H., and C. S. Keefer: Penicillin: Its antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphylococcus Aureus. *J. Clin. Investigation* **22**, 649, 1943.
- ² Keefer, C. S., R. P. Herwich, W. Van Winkle, and L. E. Putnam: New Dosage Forms of Penicillin. *J. A. M. A.* **128**, 1161, 1945.
- ³ Abraham, E. P., E. Chain, C. M. Fletcher, A. D. Gardner, N. G. Heatly, M. A. Jennings, and H. W. Florey: Further Observations on Penicillin. *Lancet* **2**, 177, 1941.
- ⁴ Foster, J. W., and H. B. Woodruff: Microbiologic Aspects of Penicillin VI Procedure for the Cup Assay of Penicillin. *J. Bact.* **47**, 43, 1944.
- ⁵ Fleming, Sir A., J. Suchet, M. Y. Young, and A. J. E. Rowe: Penicillin Content of Blood Serum. *Lancet* **2**, 621, 1944.
- ⁶ Kammelkamp, C. H. and C. S. Keefer: The Absorption, Excretion and Distribution of Penicillin. *J. Clin. Investigation* **22**, 425, 1943.
- ⁷ Cooke, J. V., and D. Goldring: The Concentration of Penicillin in Various Body Fluids During Penicillin Therapy. *J. A. M. A.* **127**, 80, 1945.
- ⁸ Barach, A. L., T. H. Silberstein, E. T. Oppenheimer, T. Hunter, and M. Soroka: Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis, and Lung Abscess: Preliminary Report. *Ann. Int. Med.* **22**, 485, 1945.
- ⁹ Herrell, W. E.: The Clinical Use of Penicillin, an Antibacterial Agent of Biologic Origin. *J. A. M. A.* **124**, 622, 1944.

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- ¹⁰ Kay, E. B., and R. H. Meade: Penicillin in the Treatment of Chronic Infections of the Lungs and Bronchi. *J. A. M. A.* **129**, 200, 1945.
- ¹¹ Mutch, N., and R. E. Rewell: Penicillin by Inhalation. *Lancet*, **1**, 650, 1945.
- ¹² Vermilye, H. N.: Aerosol Penicillin in General Practice. *J. A. M. A.* **129**, 250, 1945.
- ¹³ Meleney, T. L., B. A. Johnson, E. J. Pulaski: Treatment of Mixed Infections with Penicillin. *J. A. M. A.* **130**, 121, 1946.

DISCUSSION.—DR. JOHN H. GIBBON, JR., Philadelphia: I think this work of Doctor Adams' is very important. It brings up the whole question of whether you should use antibiotic therapy locally, or generally, or combine both methods. The only way to answer the question is to study the concentrations of the antibiotic agent in the local fluid and in the blood serum. I think Doctor Adams has shown very well that there is some value in introducing penicillin into the pleural cavity after a pneumonectomy. We have been using penicillin in this fashion routinely. In 17 pneumonectomies for carcinoma performed in the past ten months we have had one empyema, and that was due to *B. coli*.

I think his observations on aerosol penicillin are very interesting, and probably indicate that the procedure is not of great value in chronic pulmonary disease.

DR. ALFRED BLALOCK, Baltimore: I have enjoyed the report of this excellent study by Doctor Adams and his associates. I wish to ask a question about the choice of patients in whom one should use penicillin. We have given penicillin routinely preoperatively and for the first few days postoperatively to approximately 400 patients with congenital heart disease upon whom we have operated in the last two years. We have had no instances of empyema or mediastinitis in this group, and I have often wondered if the penicillin is responsible for the absence of infections. At the same time I have worried about the expense and the discomfort which the injections cause. Being somewhat superstitious in nature I have hesitated to discontinue this routine practice of giving penicillin to this group of patients. I wonder if Doctor Adams would express an opinion as to whether such injections should be given routinely.

DR. W. E. ADAMS, Chicago (closing): I do not think I am in any better position to answer Doctor Blalock's question than he is, or others here. We have felt likewise that penicillin is used more frequently than is necessary. The problem is, when to use it. If there is any possibility of respiratory function being interfered with following operative procedures, from collapse of the lung or less expansion of the lung than normal, and some likelihood of atelectasis or pneumonitis, this would be an indication to use it. These may frequently occur in thoracic surgery. We are using penicillin at the present time in all thoracic surgery and in much of our general surgery.

When we started this study we hoped that the aerosol method would prove to be more efficient than it has. All patients dislike being stuck every three hours with intramuscular injections, but since the blood serum levels of the aerosol method were so poor, we felt it was not a good substitute for the intramuscular method. At the present time we use penicillin intramuscularly to prepare patients for operation, and immediately after operation until the temperature is down to normal; following this we depend on the intrapleural method for the most part. I share Doctor Gibbon's view regarding the poor results of the aerosol method in chronic pulmonary infections.

I want to thank Doctor Gibbon and Doctor Blalock for their discussion.

STUDIES IN POSTOPERATIVE CONVALESCENCE*

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IT HAS BEEN only during the past 10 or 15 years that the surgical profession has fully appreciated the true value of proper preoperative and postoperative care in the treatment of patients undergoing operation. In general, so much more attention has been devoted to preoperative than to postoperative care that efficiency of treatment of the latter type has lagged behind. Although various therapeutic procedures carried out in preoperative care can and must be continued on into postoperative care, there are many types of therapy which are very important in the after-care of patients, but of unknown or little significance in preoperative care. Ambulation is an example of this difference in value between certain types of treatment, since it plays a much greater role in postoperative care, although all surgeons appreciate the danger of operating on patients who have been bedfast for several days before operation.

Although as long ago as 1899 Ries¹ called attention to the value of ambulation in postoperative care, its true significance was not appreciated for three or four decades. The importance of ambulation and graded exercises in shortening convalescence in military personnel was noted by Rusk,² Karpovich³ and others. However, the work done by the above authors applied primarily to convalescence from non-surgical disease. Furthermore, many of the exercises (including the Harvard step test⁴) used in the study of convalescence from diseases such as pneumonia, measles, scarlet fever, etc., cannot be utilized in surgical patients (particularly those having had a laparotomy) because of the danger of wound separation. On the other hand, ambulation can be utilized with safety in surgical patients as has been shown by the pioneer work of Powers⁵ and others during recent years.

Considerable clinical data have been accumulated up to date revealing the advantages of ambulation. Economy of hospitalization is by no means the most important advantage. A comparative study of a large series of cases by Schafer and Dragstedt⁶ has revealed a lower incidence of atelectasis and less postoperative fever in the ambulated patients. Leithauser⁷ has reported that in ambulated patients the normal vital capacity returns in two to seven days instead of seven to 14 days in patients not ambulated; he considers that "pul-

* Read before the American Surgical Association, March 26, 1947, Hot Springs, Va.

† The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Illinois.

monary complications increase in direct proportion to the reductions in vital capacities."

Elman and Akin⁸ have emphasized the deleterious effect of bed rest and malnutrition on appetite and accordingly have very aptly warned that by no means can appetite be considered an index of the patient's caloric needs. Preliminary reports on ambulation suggested that it would eliminate phlebotrombosis and pulmonary embolism. However, Powers⁵ has reported that venous thrombosis is by no means eliminated, although the incidence of fatal pulmonary embolism appears to be reduced. Burch and Fisher⁹ report two fatal pulmonary emboli in 1908 patients ambulated after abdominal operations at an army hospital. This appears to be a low incidence, but when we realize that practically all of these patients (representing a group in which pulmonary emboli are relatively infrequent) were young, it becomes obvious that these complications will not be eliminated by ambulation. Numerous observers have reported an improvement in wound healing with a lowered incidence of wound disruption.

The presence of a negative nitrogen balance in convalescing patients has long been known. Cuthbertson's¹⁰ early observations (1932) that the nitrogen excretion on the first postoperative day is low has been confirmed by the authors and others. Cuthbertson reported further that the negative nitrogen balance following operation exceeded that observed during starvation, indicating that lack or decrease of food intake was not the only factor giving rise to a negative nitrogen balance in patients convalescing from operation. Merely confinement to bed has been shown to result in a negative nitrogen balance (Keys¹¹). Elman and associates⁸ and Co Tui and associates¹² have called attention to the fact that the postoperative negative nitrogen balance in patients can be prevented by force feeding with proteins and parenteral administration of amino acids. However, it is well known that a simple order to force feedings in patients immediately postoperatively cannot solve the problem of negative nitrogen balance because of the gastric and intestinal atony so commonly observed following laparotomy. The conclusion expressed by Ivy and Grossman¹³ that "the best means for increasing gastric tone and motility is physical exercise" can be supported by all observers studying patients during postoperative convalescence.

PURPOSE OF EXPERIMENTS

Unfortunately the pendulum always swings too far when a new form of therapy is introduced; unquestionably many patients are harmed in vigorous ambulation programs, by the uncontrolled efforts of some surgeons not too well informed on physiologic functions and the inadequate reserves of their patients. As a matter of fact, very little data are available at the present time to indicate which patients should not be ambulated, and how much ambulation should be prescribed. Furthermore, ambulation is only one of innumerable forms of treatment which might be instituted to improve the rate of post-

operative convalescence. We are already becoming aware of the great value of a high protein intake (Elman), and liberal quantities of blood. Other factors, including chemotherapy, physiotherapy, psychotherapy, etc., are important in convalescence but without doubt many other types of therapy still unknown may aid greatly in the speed of recovery from operations.

However, we cannot expect other important discoveries to be made in the field of postoperative convalescence without first getting more data as to what physiologic functions are impaired and how. Perhaps one of the most important questions to solve is the explanation of the extreme weakness so prevalent following major operations, particularly in people past middle age. Inadequate diet will explain many decrements, as will be discussed later, but is not the major factor in explanation of this manifestation, which is probably the most important one retarding convalescence. Has the cardiac reserve been impaired sufficiently to explain this weakness and fatigue? At present there is inadequate evidence to explain these symptoms on that basis. Has the content of glycogen or other tissue constituents in the muscle been disturbed sufficiently to explain them? Could impairment of such organs as the liver, adrenal glands, etc., explain them? It is obvious that the true explanation is unknown.

For reasons discussed above there is an obvious need for the study of (1) the functions of various organs during convalescence and (2) additional factors in therapy which may prevent the various insufficiencies produced by major operations. It is for these reasons that the experiments herein discussed were undertaken.

DESCRIPTION OF TYPES OF THERAPY

DIVISION OF PATIENTS INTO GROUPS—In our efforts to determine what types of therapy might improve the rate of convalescence we divided the patients into a number of groups, each of which varied in the type of therapy. The first 14 groups listed below consisted entirely of patients having herniotomy; most of these patients were relatively young men. The last two groups consisted of patients having cholecystectomy. All groups not designated as "full diet daily" had no oral feeding the day of the operation, and 1/4, 2/4, 3/4 and 4/4 of their diet on the first 4 postoperative days respectively.

(I.) *Control hospital group*.—This group of patients was chosen from the surgical floor and served to furnish scout data. None of these data were utilized in actual computation of results in the various groups.

(II.) *Control Experiment Group*.—In utilizing data described in Group I, we decided that the diet for our control patients should contain basal calories plus 20 per cent, 15 per cent* of which were derived from protein. This might be considered barely sufficient for maintenance.

(III.) *"Shotgun" Group: Supplements,** basal diet plus 100 per cent with 20 per cent protein, full diet daily, ambulation.†*—In planning for the treatment of this group the objective was to furnish all factors that might conceivably influence convalescence favorably. The diet consisted of basal calories plus 100 per cent, with 20 per cent of the calories from protein. This diet was served preoperatively in the form of meals. On the day of operation and on the succeeding postoperative days, until the patient was again able to eat, it was given in the form of a tube feeding. This insured the maintenance of the nutrition at a constant level.

* The figure designating percentage protein refers to per cent calories, not weight.

** Data on the quantity of the various supplements will be included in another publication in preparation.

† All groups not designated "ambulation" were not ambulated.

POSTOPERATIVE CONVALESCENCE

Preoperatively the diet contained the following supplements: choline, vitamin B complex from yeast, Ascorbic acid, Vitamin A and Vitamin D. On the day of surgery and on the four succeeding postoperative days the following supplements were given parenterally: Vitamin K, Liver extract (2 units to 1 cc.), Adrenal cortical extract, Testosterone propionate, Thiamine chloride, Riboflavin, Pyridoxine, Calcium pantothenate, Nicotinamide, Ascorbic acid and Choline.

In addition to the above supplements, methionine and 5 per cent amigen solution in 5 per cent glucose (2000 cc. intravenously) were given on the day of surgery. This group received ambulation. Early in the study of this group it was obvious that the "Shotgun" group had reacted favorably to the treatment. Consequently, the groups described below were set up to analyze the factor or factors responsible for this favorable effect.

(IV.) *Basal Calories Plus 20 per cent, 15 per cent Protein, Spinal Anesthesia.*—This group was maintained in bed without any form of exercise. The effect of inhalation anesthesia was eliminated.

(V.) *Basal Calories Plus 20 per cent, 15 per cent Protein, Spinal Anesthesia, Modified Ambulation.*—These patients received push-up, step-up and psychomotor tests. It is realized that this program gave the patients a certain amount of ambulation.

(VI.) *Basal Calories Plus 20 per cent, 15 per cent Protein, Ambulation.*

(VII.) *Basal Calories Plus 20 per cent, 15 per cent Protein (Full diet given each day, by tube for first few postoperative days).*

(VIII.) *Basal Calories Plus 20 per cent, 15 per cent Protein, Supplementation.*—The supplements were the same as those described above under "shotgun" group (III) except that vitamin K, 4 mg., was administered throughout the hospital stay.

(IX.) *Basal Calories Plus 20 per cent, 15 per cent Protein, Methionine.* Two grams of methionine was administered daily from the date of entrance.

(X.) *Basal Calories Plus 20 per cent, 15 per cent Protein, No Surgery.* These patients were kept in bed, given the same food, fluid, and sedation as group II but herniorrhaphy was omitted. The patients were quite young, 16 to 17 years of age, which suggests that they may not be entirely comparable with the other groups.

(XI.) *Basal Calories Plus 20 per cent, 40 per cent Protein (Full diet given for each day, by tube for first few postoperative days).* This diet increased rather sharply the protein intake. It ranged between 182 and 233 Gm. with an average value of 201 grams.

(XII.) *Basal Calories Plus 20 per cent, 40 per cent Protein (Full diet given each day, by tube for first few postoperative days), Ambulation.*

(XIII.) *Basal Calories Plus 100 per cent with Protein at the Control Level.* This group was planned to test out the effect of excess calories from sources other than protein. The protein was the same as that in the control diet containing basal calories plus 20 per cent. Since the calories in the diet were increased, the distribution of the constituent factors was altered. The diet now derived 10 per cent of its calories from protein and 40 per cent from fat. On the day of surgery the patients received no protein, on the first postoperative day 1/4, second, 2/4, third, 3/4, and fourth, 4/4 of the prescribed daily protein.

(XIV.) *Basal Calories Plus 40 per cent, 15 per cent Protein.* This group was composed of women having herniotomy who were placed on the regime used in patients submitted to cholecystectomy. This plan furnished an opportunity to make a comparison of the relative loads of cholecystectomy and herniotomy. More specifically, it served as a control group for the later studies in alterations in serum proteins found in patients undergoing cholecystectomy.

(XV.) *Cholecystectomy, Basal diet plus 40 per cent, 15 per cent Protein, General Anesthesia.*—This group might be considered the control group for cholecystectomy.

(XVI.) *Cholecystectomy, Basal diet plus 40 per cent, 15 per cent Protein, Spinal Anesthesia.* This group is the same as XV except that spinal anesthesia was used instead of ether anesthesia.

EXPERIMENTAL METHODS

In the experiments herein discussed, we have limited our study to patients having herniotomy or cholecystectomy. Studies are also being made in other types of operations, particularly those in which more operative work is required—(e.g. gastrectomy). However, most of the work was done on patients having herniotomy because they lend themselves so well to experimental study, the preoperative condition of the patient is so stabilized, and the amount of operative work so nearly equal in all cases. The preoperative period consisted of 4 to 7 days and was devoted to tests on the patients and

to stabilization of their diet. The control group of patients was allowed out of bed on the 10th postoperative day and discharged on the 12th day. Those in the other groups, who did not receive ambulation, were out of bed on the 6th postoperative day and were discharged on the 7th day. Those who received ambulation were out of bed on the 1st postoperative day and discharged on the 7th day.

DIETARY MANAGEMENT AND FLUIDS—Large quantities of basic foods were procured, analyzed for nitrogen, weighed and placed in a deep freeze unit maintained at minus 10°F. Tube feedings consisted primarily of evaporated milk, skimmed milk powder, amigen and dextrose. Low protein diet consisted of salad oil (one egg yolk per 200 cc.), glucose and water; it containing 3.2 Gm. protein and 3020 calories per liter.

Herniotomy.—On the day of operation the control herniotomy patients were given 1000 cc. of physiologic saline and 1000 cc. of 5 per cent glucose intravenously; nothing was given by mouth. On the succeeding days they were given 1/4, 1/2, 3/4 and 4/4, respectively, of their postoperative diet.

Cholecystectomy.—A stomach tube was inserted for decompression; it was removed at the end of the second postoperative day. On the day of the operation the cholecystectomy patient received 1000 cc. of 5 per cent glucose in physiologic saline and 2000 cc. of 5 per cent glucose intravenously. The same fluids were given on the first and second postoperative day except that when the amount of fluid aspirated from the stomach exceeded 500 cc. per day, an amount of 5 per cent glucose with saline was given to equal the excess beyond 500 cc. On the third postoperative day the patient received 1000 cc. of 5 per cent glucose or physiologic saline intravenously and 600 calories by mouth. The diet was increased 600 calories per day until the patient was receiving his preoperative diet, i.e. basal diet plus 40 per cent.

EXERCISE AND AMBULATION.—In the group of patients subjected to ambulation we added calisthenics similar to those described by Stafford, DeCook and Picard.¹⁴ Preoperatively the patients were given calisthenics for 21 minutes each day, divided into two periods. Postoperatively they were given calisthenics for 20 minutes divided into 2 periods. The "sit-up" exercises which were given preoperatively were omitted postoperatively because of the danger of damage to the wound. In addition to the calisthenics the patient was out of bed each day for a period increasing with each postoperative day.

ANESTHESIA.—General anesthesia consisted of nitrous oxide and ether administration. Tracheal intubation was used uniformly. The same preoperative medication was utilized in all cases, namely morphine and scopolamine. Pontocain was used for spinal anesthesia.

TESTS UTILIZED.—Innumerable tests were chosen to be carried out on the patients, but preliminary work proved many of them unsatisfactory for several and varied reasons.

Liver function tests.—The *urobilinogen test*, as performed by Watson, proved to be one of the most satisfactory tests of liver function. The test depends upon the quantitative excretion of urobilinogen in the urine, expressed in milligrams excreted in 24 hours.

The *bromsulphalein test* was also effective in determination of the hepatic function. Five milligrams per kilo of body weight of bromsulphalein were injected intravenously and samples of blood drawn at 30 minutes and at 40 minutes. The sum of these two readings was chosen as the method of arriving at one figure for recording results of the tests. Postoperative values were expressed in terms of percentage of normal preoperative efficiency.

Numerous miscellaneous tests of liver function were used. The *prothrombin test* (Quick) was utilized, and as illustrated later, yielded information of variable value. The *cephalin flocculation test*, the *hippuric acid test*, the *galactose tolerance test* and *bilirubin excretion test* were used but did not appear satisfactory or adaptable for our purpose and were abandoned after preliminary trial. The two-dose *Exton-Rose glucose tolerance test* was also utilized but not found adaptable except in the patients submitted to cholecystectomy. Blood sugar was determined in the fasting state and at the end of one-half hour, one hour and two hours after the first dose of glucose.

Metabolic tests.—Nitrogen balance studies were carried out on all patients and, as has been shown by numerous authors, proved to be of great value. The nitrogen in the urine and food was determined by the macrokjeldahl method with titration of the ammonia. In computing the nitrogen balance, it was assumed that the fecal nitrogen was equal to 10 per cent of the ingested nitrogen.

Serum total proteins, serum albumin and serum globulin were determined in only one group of patients submitted to herniotomy but in both groups submitted to cholecystectomy. These determinations were made by standard procedures.

Serum total cholesterol and cholesterol esters were determined by using digitonine separation technic.

POSTOPERATIVE CONVALESCENCE

The determination of 17-ketosteroids was carried out after the technic described by Robbie and Gibson.

Quantitative tests were performed for creatinine and creatin excretion, but as indicated later results yielded no significant data.

Circulatory efficiency and muscular fitness.—A tilt-table test was carried out on several groups of patients. The procedure and method for scoring performance will be described in a paper soon to be published.

Recently a modification of the flarimeter and Flack test has been used* to study cardiovascular reserve or function. In general, the procedure consists of determining the cardiovascular response to an increase in intrapulmonary pressure obtained by having the patient blow against a resistance of a column of mercury, and maintaining this pressure for a specified period of time. Blowing in this manner exerts pressure on the thin-walled superior and inferior vena cavae, and on the pulmonary veins, thus interfering with the filling of the right and left auricles respectively. It would appear that this procedure would test the ability of the vascular system to compensate for a reduced cardiac output brought about by obstruction to the flow of blood through the vena cavae and pulmonary veins.

All tests were performed one hour or more after breakfast and immediately following one half-hour of complete bed rest. The procedure was carried out with the patient in two positions, namely, supine on the tilt-table, and then with the tilt-table tilted to an angle of 60°. The apparatus consists of a mouthpiece attached by appropriate thick-walled rubber tubing attached to an aneroid manometer possessing a large recording dial, which the patient may observe, thus aiding him in maintaining the required level of pressure. A side tube was introduced into the system, the free end of which was filled by a metal disk containing an opening $\frac{1}{4}$ inch in diameter. This vent for a constant escape of air is necessary to prevent the patient from maintaining the pressure with the muscles of his mouth or pharynx.

After obtaining a series of control blood pressure and pulse rate readings in the supine position, the patient is instructed to take a very deep inspiration and blow into the system to raise the pressure to the desired level of either 20 or 30 mm. Hg. In each instance the patient continues to blow for 25 seconds. Blood pressure readings are obtained at the end of 10 and at the end of 20 seconds of blowing, immediately after the procedure is terminated, 20 seconds later and, if necessary, 1 minute later. Instead of recording pulse rates during the period of blowing and in the period of recovery, a more accurate count can be obtained by using Lead II of the electrocardiograph. The test is repeated with the patient tilted at an angle of 60°.

A push-up test was devised to obtain readings following strenuous exercise of the upper extremities which would not endanger the abdominal wound. A weight lifting apparatus on a frame was designed to fit over the bed so that the patient could lie on his back and push up two weights of 20 pounds each. The weights were raised at the rate of 30 times per minute for two minutes. In scoring the test the resting pulse rate was compared with the pulse rate obtained at 5 second intervals for 3 minutes, starting 5 seconds after the end of the test. The difference between the resting pulse rate and the rate obtained between the interval of 5 to 35 seconds and 60 to 90 seconds was recorded as the result of the test. The apparatus could be used as a form of ambulation, or as a test for circulatory efficiency. When used as a test, it was applied three or four times preoperatively, on the first postoperative day and continued on succeeding days.

The flarimeter test was performed on a few groups of patients. The patient took three long preliminary inspirations and expirations. He then inspired maximally and at the 4th expiration maintained an expiratory pressure of 40 mm. mercury as long as possible. This is a different test than the modified flarimeter-Flack test previously described.

The vital capacity was determined by a Collins Spirometer on a few groups of patients.

The strength of hand grip was determined by the Smedley hand dynamometer. The highest of four trials given at 30 second intervals was used as the maximum. Endurance time was also determined with the dynamometer. This represented the length of time the patient could maintain a grip equal to 40 per cent of the maximum strength of the hand grip.

Psychomotor tests.—Tests including steadiness of hand, speed of tapping, simple choice reaction time and coordination time were done on many patients with herniotomy, but since the results were insignificant the tests were discarded early in our

* Tests modified by Dr. David Abramson, who has recently joined our group studying convalescence.

studies. For a time we utilized the critical fusion frequency of flicker test as a measure of determining fatigue of the retino-cortical system. Results of this test were likewise of no statistical significance.

STATISTICAL ANALYSIS.—All data were submitted to a statistical analysis. Whenever the term "significant" is used in the text, it is applied in the statistical sense.

RESULTS

LIVER FUNCTION TESTS.—Of the numerous liver function tests used in our studies, the urobilinogen and bromsulphalein tests were of the most value.

Urobilinogen Test.—The average preoperative value for 92 patients with hernias was 1.61 mg. for 24 hours. Only 2 had a preoperative value of more than 4 mg. The average preoperative level in 10 patients with cholecystitis was 1.19 mg. We found that the postoperative level was influenced sharply by the preoperative level. It therefore appeared most accurate to express the postoperative urobilinogen excretion in terms of a percentage efficiency based upon the preoperative value; the figure was obtained by dividing the preoperative value by the postoperative value and multiplying by 100. The values of the first 5 postoperative days were averaged to obtain the individual score. The values of all the patients in each group were averaged to give a numerical value for the group.

In the groups having ambulation or a high percentage of protein in their diet the postoperative excretion of urobilinogen remained at levels considered to be within normal limits or near normal. Table I reveals that the best score in the hernia patients was made by the "shotgun" group, which had received numerous supplements and a basal diet plus 100 per cent with 20 per cent protein. The percentage efficiency in this group was 100 compared to 60 in the control group operated on for herniotomy without any special therapy.

TABLE I

Scores and ranks of the groups of patients with herniotomy, based upon postoperative values expressed as percentage of preoperative values for urobilinogen, bromsulphalein and tilt table, and upon nitrogen balance in grams over a period of six days.

Group No.	No. of Pts.	Management	Urobilinogen Excretion (Rank)	Bromsulphalein Retention (Rank)	20-Minute Tilt Table Response (Rank)	6-Day Nitrogen Balance (Rank)	Final (Rank)
XII	5	B + 20%, 40% protein; ambulation; tube fed*	86 (3)	89 (1)	103 (3)	19.4 (1)	1
III	5	"Shotgun" B + 100%, 20% protein; tube fed; supplements; ambulation	109 (1)	66 (4)	123 (2)	10.2 (2)	2
VI	7	B + 20%, 15% protein; ambulation	61 (6½)	68 (3)	129 (1)	-21.3 (7)	3
XI	7	B + 20%, 40% protein; tube fed*	96 (2)	54 (9)	84 (4)	7.6 (3)	4
VII	6	B + 20%, 15% protein; tube fed*	61 (6½)	66 (4)	80 (5)	-13.8 (4)	5
IV	6	B + 20%, 15% protein; spinal anesthesia	86 (3)	74 (2)	71 (9)	-31.3 (10)	6
XIV	4	B + 40%, 15% protein; gallbladder post-operative regime	60 (8)	47 (10)	73 (7½)	-16.2 (5)	7½
VIII	7	B + 20%, 15% protein; supplementation	64 (5)	63 (6)	54 (10)	-29.8 (9)	7½
IX	4	B + 20%, 15% protein; methionine	40 (10)	61 (7)	78 (6)	-24.3 (8)	9
XIII	3	B + 100%, 10% protein; tube fed*	29 (11)	40 (11)	73 (7½)	-17.5 (6)	10
II	10	Control, B + 20%, 15% protein	60 (8)	60 (8)	50 (11)	-31.4 (10)	11
I	22	Control on hospital diet*	69
V	7	B + 20%, 15% protein; spinal anesthesia; modified ambulation†	104	65

The figures in parenthesis after each column represents rank of efficiency of treatment in that group as compared to others.

B = Basal diet. * Tube fed = A full diet was given every day (by stomach tube for first 4 postoperative days), including day of operation. † Not included in ranking.

POSTOPERATIVE CONVALESCENCE

In the 5 patients having cholecystectomy which were used as controls (ether anesthesia) the efficiency score was only 48 compared to an average of 60 in the hernia controls, thus indicating a greater load in cholecystectomy than in herniotomy; in this small series of gallbladder patients, those operated on with spinal anesthesia showed less hepatic impairment than patients given ether.

In Table II designed to show the effect of complications on urobilinogen excretion, the figures are expressed in mg. per 24 hours, but not all groups are included. Under each complication is given the average for the group in which the patient with the complication

TABLE II
Urobilinogen Excretion in Mg. Per 24 Hours in Patients with Complications

Complication	Preoperative Average (Mg.)	Postoperative Day				
		1	2	3	4	5
Stitch abscess.....	1.9	4.5	14.9	36.4	45.7	27.8
Control group IX*.....	1.4	2.9	10.1	9.5	5.8	3.4
Wound infection.....	1.2	3.1	40.7	44.0	90.2	9.7
Control group III*.....	1.1	0.9	1.2	2.2	2.3	1.8
Pneumonia.....	1.1	19.3	17.0	6.7	3.3	2.4
Control group XI*.....	2.3	3.5	4.8	3.5	2.7	2.6
Atelectasis pneumonitis.....	6.7	15.4	18.6	2.8	2.1	1.5
Control group II*.....	2.6	3.9	4.6	5.5	6.3	4.7
Cystitis.....	1.8	1.4	5.9	16.7	8.2	
Control group IX*.....	1.4	2.9	10.1	9.5	5.8	3.4
Coronary thrombosis.....	1.9	1.6	6.3	6.2	9.1	9.4
Control group VIII*.....	1.3	2.1	2.5	3.0	2.6	2.4

* Other members of same diet group who suffered no complications.

was originally placed. The marked increase in urinary excretion of urobilinogen in patients with complications is striking. These results suggest that although the operation itself inflicts a definite load upon the liver, most postoperative complications inflict still a greater load. The marked impairment in complications suggests that the test is a valuable index of hepatic efficiency.

Another reason for considering the urobilinogen test an efficient one is the fact that the excretion remained above normal for 6 to 8 days postoperatively. The maximum was usually noted on the 2nd postoperative day. Improvement was gradual until the normal figure was regained.

Bromsulphalein Test.—Tests were run two times preoperatively and on the first, third and fifth postoperative days. Postoperative values were expressed in terms of percentage of normal preoperative efficiency.

Postoperative retention returned to normal by the fourth or fifth day contrasted to the persistence of abnormal excretion of urobilinogen for 6 to 8 days postoperatively.

As was revealed by the urobilinogen test, ambulation and a diet with a high protein content reduced the postoperative impairment to a very low figure.

TABLE III
Urobilinogen Excretion in Control Patients Having Operation (Group II) Compared to Excretion in Patients Put Through Same Regime Without Operation (Group X)

Group Number	Management	Av. Pre-Op. Excretion in Mg. Per 24 Hrs.	Preoperative Per Cent of Postoperative Value Days of Postoperative Regime					
			1	2	3	4	5	6
II	Control.....	2.59	77	75	45	48	57	100
	Basal diet +20%..... (Av. of 10 pts.)							
X	15% protein.....							
	Basal diet +20%.....	.69	12	9	13	75	65	
	15% protein.....	.86	34	44	56	506	261	
	Sedation.....	1.02	19	76				
	No operation (4 patients)	.72	24	28				

TABLE IV
Nitrogen Balance (In Grams) in Patients With Complications (Including the Day of
Operation and 5 Succeeding Days)

Complication	Preoperative		Postoperative	
	Patient	Control*	Patient	Control*
Stitch abscess.....	-2.78	+2.80	-71.50	-24.29
Wound infection.....	+9.72	+4.16	-30.09	+10.24
Pneumonia.....	+3.57	+5.55	- 9.79	+ 7.62
Atelectasis.....	-2.49	-2.30	-49.86	-31.44
Cystitis.....	-0.85	+2.80	-39.57	-22.75
Coronary thrombosis.....	-0.55	-1.46	-25.30	-29.81

* Other members of same diet group who suffered no complications.

Table I reveals the best score in Group XII (Basal diet plus 20 per cent, 40 per cent protein and ambulation). The score in this group was 89 per cent of the preoperative efficiency as compared to 60 per cent in the control group (II). The fact that the degree of change in postoperative figures over preoperative figures was much less pronounced than with the urobilinogen test suggests that the urobilinogen test is superior to the bromsulphalein test as an indication of hepatic function. As in the urobilinogen test, there was a decrease in efficiency of liver function in patients with complications, but the degree of inefficiency was much more marked in the urobilinogen test.

Miscellaneous Tests of Liver Function.—The *prothrombin test* in herniotomies revealed little positive information except a slightly greater tendency to remain nearer normal in patients having spinal anesthesia than in those having nitrous oxide and ether. The *Exton-Rose glucose tolerance* test revealed higher blood sugar curves postoperatively than preoperatively but there was little difference between the two groups in which it was used; the test was therefore considered to be of only slight value in our experiments. The *hippuric acid test*, *cephalin flocculation test*, *excretion time for bilirubin*, and the *galactose tolerance test* were used but were abandoned as not being as suitable or reliable as the urobilinogen and bromsulphalein tests.

METABOLIC TESTS.—Of the various tests in this group the most significant results were obtained in those dealing directly with the metabolism of proteins.

Nitrogen balance studies.—Analysis of figures on nitrogen balance reveal one major fact, namely that regardless of the procedures utilized to abolish decrements, a negative balance cannot be averted unless the patient is getting a certain amount of protein. It is admitted, however, that a high carbohydrate or fat diet will have a tendency to spare protein.

In Table V, the data showing the effect of ambulation and slight deviation in diet on nitrogen balance is summarized. In Category A, the diet, basal plus 20 per cent with 15 per cent protein, was carried out without deviation in the group which was not ambulated, as well as in the ambulated group. In the former group the nitrogen loss for the 6-day postoperative period was 31.4 Gm. compared to a loss of 21.3 Gm. for the latter group, indicating that ambulation actually tends to decrease the nitrogen loss. The favorable effect is further substantiated by Category B containing 2 groups placed on identical diets, i.e. basal diet plus 20 per cent with 40 per cent protein. The first group was not ambulated; the second group was ambulated. The nitrogen gain was greater in the ambulated group, being 19.4 Gm. for the 6-day period, compared to 7.6 Gm. for the non-ambulated group. In another series, designated as Category C, in which the diet was basal plus 20 per cent with 15 per cent protein for each group, a comparison is not valid because the ambulated group (VI) received only a partial diet during the first 4 postoperative days; this data merely indicates that ambulation is no substitute for protein or food. Analysis of the other two groups illustrated in Table V indicate quite clearly that ambulation tends to decrease nitrogen loss.

POSTOPERATIVE CONVALESCENCE

A comparison of the figures on nitrogen balance between groups IV and II in Table I indicates that spinal anesthesia has no sparing effect on nitrogen. Each group had the same diet, all therapy being the same except that Group IV had spinal anesthesia while Group II had gas-ether anesthesia. The nitrogen loss was identical, being 31.3 and 31.4 Gm. respectively for the 6-day period. This conclusion is substantiated by the two group studies in patients having cholecystectomy. Each of the 2 groups had the same diet

TABLE V
Effect of Ambulation and Slight Deviation of Diet on Nitrogen Balance

Category	Diet		6 Day Nitrogen Balance
A	Basal diet +20% 15% protein	(Group II) (No ambulation)	-31.4 Gm.
	Partial diet First 4 P. O. days	(Group VI) ambulation	-21.3 Gm.
B	Basal diet +20% 40% protein	(Group XI) no ambulation	7.6 Gm.
	Full diet daily	(Group XII) ambulation	19.4 Gm.
C	Basal diet +20% 15% Protein	(Group VII) no ambulation Full diet daily	-13.8 Gm.
		(Group VI) ambulation Partial diet first 3 P. O. days	-21.3 Gm.

(namely basal plus 40 per cent with 15 per cent protein) and all other factors equal except that one had spinal and the other gas-ether anesthesia. The nitrogen loss in the two groups was almost identical, being 31.1 and 29.0 Gm. respectively for the 6-day period.

Serum total protein; albumin and globulin.—Realizing that an herniotomy was probably not a sufficient operative load to produce a decrease in serum proteins, we analyzed the blood for protein in only one group of hernia patients, namely those having a basal diet plus 40 per cent, 15 per cent protein (Group XIV). The postoperative decline in serum albumin and total protein was of statistical significance on the third day (see Table IV), but was only 13 and 9 per cent respectively below the preoperative level.

However, following cholecystectomy the reduction was of definite statistical and clinical significance (see Table VI). In the group having ether anesthesia, the serum albumin declined gradually until by the 11th day the value was only 75 percent of the preoperative figure. The reduction in this group was definitely greater than in the group

TABLE VI
Postoperative Changes in Serum Total Protein, Albumin and Globulin, Expressed in Percentage of Preoperative Level of Patients Submitted to Cholecystectomy and Herniotomy

Group Number	Management	Preoperative Avg. in Gm./100 cc.	Percent Pre-Op. Level Postoperative Day			
			3	5	7	11
XV Chole- cystectomy	Basal diet +40%	Total Protein 6.47	92	...	90	89
	15% protein	Albumin 3.87	84	...	78	75
	Ether anes.	Globulin 2.60	105	...	106	107
XVI Chole- cystectomy	Basal diet +40%	Total Protein 6.59	91	92	95	97
	15% protein	Albumin 4.14	82	82	87	91
	Spinal anes.	Globulin 2.45	106	110	110	107
XIV Herniotomy	Basal diet +40%	Total Protein 6.75	91	93		
	15% protein	Albumin 4.26	87	89		
	Gallbladder postoperative regime	Globulin 2.49	98	98		

having spinal anesthesia. In the latter group, there was a tendency toward an early recovery; by the 11th postoperative day the value had risen to 91 per cent of the preoperative level. In the former group recovery was slow, several weeks elapsing before the preoperative level was reached. The data indicate that ether anesthesia had a greater detrimental effect on blood protein than spinal anesthesia.

In each group the globulin content rose slightly but not significantly, showing a slight tendency toward an A/G reversal; these findings support previous data revealing hepatic damage inflicted by operation.

Serum total cholesterol and cholesterol esters.—Cholesterol determinations were made in one group of patients having herniotomy, namely Group XIV, which had basal diet plus 40 per cent, 15 per cent protein, with no supplements. The values for total cholesterol

TABLE VII
Changes of Total Cholesterol, Cholesterol Esters and Percent Cholesterol Esters in Patients Submitted to Cholecystectomy and Herniorrhaphy

Group Number	Management	Preoperative Average in mg./100 cc.		Postoperative Average Day			
				3	5	7	11
XV	Cholecystectomy	Total cholesterol	254	193	...	213	229
	Basal diet +40%	Cholesterol esters	199	103	...	145	191
	15% protein	% cholesterol esters	78.5	53.4	...	68.1	83.4
	Ether anesthesia						
XVI	Cholecystectomy	Total cholesterol	265	202	212	212	200
	Basal diet +40%	Cholesterol esters	212	162	165	178	171
	15% protein	% cholesterol esters	79.3	80.2	77.8	84.0	85.5
	Spinal anesthesia						
XIV	Herniotomy	Total cholesterol	246	224	238		
	Basal diet +40%	Cholesterol esters	216	185	208		
	15% protein	% cholesterol esters	87.8	82.6	87.4		

and cholesterol esters were significantly lower only on the third postoperative day (see Table VII).

In the patients having cholecystectomy there was a definite decline in the total cholesterol and cholesterol esters in both groups which were treated the same except for ether anesthesia in one group and spinal in the other. The difference between the readings of the two groups was too slight to be of statistical significance except that the spinal anesthesia group showed definitely less decrease in per cent cholesterol esters on the third postoperative day ($P=0.008$) and probably less on the seventh postoperative day.

Miscellaneous metabolic tests.—Studies on the excretion of 17-ketosteroids were made on Groups II, III and V of the herniotomy series. There was considerable individual variation and a wide daily fluctuation. Changes of statistical significance occurred, but they appeared to have little if any clinical significance. Thus Group V showed a definite decrease on the day of operation and on the first postoperative day ($P=0.0005$ and $P=0.0168$, respectively). The significance of the difference disappeared by the second postoperative day. On the other hand, in Group III, which received daily intramuscular injections of 10 mg. testosterone propionate in oil, there was no true difference between the preoperative value and that on the day of operation.

Studies were made in creatine excretion in groups I, II, III and V of the herniotomy series. Differences of statistical significance were revealed but no clinical value could be attributed to the results except that the preoperative excretion in Group III, which received large quantities of protein, is definitely higher than in Group I, and insignificantly higher than in Group II. In all groups except Group III the postoperative excretion was decreased compared to the preoperative level, but only on the day of surgery and the first postoperative day.

POSTOPERATIVE CONVALESCENCE

In Groups II, IV and V of the herniotomy series, studies were carried out on *creatinine excretion*. No changes of statistical significance were detected except for an increase in the creatinine coefficients in Group III on the first postoperative day.

TESTS FOR CIRCULATORY EFFICIENCY AND MUSCULAR FITNESS.—In this study of postoperative convalescence we have been limited in our choice of tests because many of them previously demonstrated by other investigation to be of value in studying convalescence were too strenuous to apply to patients with fresh operative wounds of the abdomen.

Tilt-Table Test.—This test has been used by numerous investigators in studies on physical fitness and has yielded valuable information on the effect of posture (pooling of blood) on blood pressure and pulse. Since the test is designed to show the effect of blood pooling on blood pressure and pulse, it presumably should test primarily the efficiency of circulatory functions. A new method of converting the readings obtained into one score for the patient will be published elsewhere. Conversion of the numerous readings into one score was essential if patients in one group are to be compared to patients in another group.

In the herniotomy patients, the three groups which were ambulated (Groups VI, III and XII) had the best tilt-table scores (see Table I) having a rank of 1, 2 and 3 respectively in the 11 groups having tilt-table tests. The beneficial effect of ambulation can be proved by comparison of the three groups mentioned with other groups not receiving ambulation or with other groups not receiving ambulation but receiving more calories. For example Group VII (not ambulated) received more food than Group VI (during the first 4 postoperative days only) but had a tilt-table rank of 5 compared to a rank of 1 for Group VI which was ambulated. Group XI which was not ambulated had a tilt-table rank of 4, compared to a rank of 3 for group XII which was ambulated; except for ambulation, treatment was identical in these two groups.

In the patients having cholecystectomy, there was no significant difference between the two groups (XV and XVI) which differed only in the fact that ether anesthesia was used in one group and spinal in the other.

Modified flarimeter and Flack Test.—With few exceptions, the systolic blood pressure preoperatively dropped 10 to 20 mm. after 25 seconds of blowing against a pressure of 20 or 30 mm. of mercury, but at the end of the blowing period there was a sharp rise in pressure varying from 38 to 73 mm. The rise was greater when the patient was blowing against 30 mm. mercury, and when he was tested in a tilted position (i.e. on the tilt-table).

As in most other tests, the postoperative performance was compared to results obtained preoperatively.

In 15 patients tested the reaction following blowing against 20 mm. of mercury in the horizontal position had returned to normal in only one patient by the 3rd postoperative day. All patients in this category showed a normal response by the 8th or 10th day.

Six patients were tested in the tilted position, blowing against 20 mm. of mercury. On the 3rd postoperative day the readings were normal on none of the patients. By the 10th postoperative day the readings on five had returned to normal; the response in one patient remained abnormal until the 20th day.

The response to blowing against 30 mm. of mercury was similar to that just described except that some of the patients were unable to perform the test on the 3rd postoperative day. The delay in return to normal was slightly greater in this group; by the 11th day the response in two was still abnormal.

Push-up test.—This test was used in four groups of patients having herniotomy: There was a remarkable consistency in the pulse rate 5 to 35 seconds and 60 to 90 seconds after termination of the test in all groups preoperatively; the pulse rate was elevated 19 and 11 or 12 beats per minute in the two periods respectively (See Table VIII). Postoperatively there was fair uniformity in Groups XII, VI and III, all of which were ambulated; the smallest increase in pulse rate was noted in Group XII which was ambulated and received a diet in which 40 per cent of the calories were derived from

TABLE VIII

Push-Up Test. The Per Minute Difference Between the Resting (Recumbent) Pulse Rate at 5 to 35 Seconds and 60 to 90 Seconds After the Test. The Test Required the Patient to Elevate Weights of 40 Pounds a Distance of 1 Foot, 30 Times Per Minute for 2 Minutes. All Groups Listed Are in Patients Having Herniotomy

Number	Management	Postoperative Average								
		Preoperative Average			1st Day			2nd Day		
		Resting Pulse Rate	5-35 Seconds	60-90 Seconds	Resting Pulse Rate	5-35 Seconds	60-90 Seconds	Resting Pulse Rate	5-35 Seconds	60-90 Seconds
XII	B +20%, 40% protein, tube fed, ambulation	66	+19	+12	87	+14	+7	76	+15	+6
VI	B +20%, 15% protein, ambulation	63	+19	+12	68	+18	+7	66	+18	+9
III	"Shot-Gun" B +100%, 20% protein, tube fed, supplements and ambulation	78	+19	+11	98	+19	+13	93	+13	+8
V	B +20%, 15% protein, spinal anesthesia; no ambulation, but mild exercise with certain tests	70	+19	+11	74	+28	+19	67	+29	+15

protein. In Group V which was not ambulated, the average rise in pulse rate on the first postoperative day was 28 and 19 for the two periods compared to 19 and 11 for the preoperative figures. These data show a tendency toward a greater degree of tachycardia following exercise with the push-up test, when the patient was not ambulated, and received a low protein diet. The test was not used with patients with cholecystectomy.

In the push-up test as well as several others herein described, we are relying upon the response of the heart rate to exercise as being an index of physical fitness. Taylor and Brozek¹⁵ remark that "the heart rate after a standard amount of work is probably the most useful single criterion of fitness in the study of convalescence." Unfortunately we know little about the physiologic mechanisms giving rise to the increase in pulse rate, but until these factors are known valuable data may nevertheless be discovered concerning methods of measuring and improving physical fitness.

Stair Climbing Test.—This test was used in three groups of patients with herniotomy, namely XII, VI and XIII as indicated in Table IX. As might be expected, the results were similar to those obtained in the push-up test. The best results were obtained in the group of patients with ambulation, and 40 per cent protein in their diet. The poorest results were obtained in the non-ambulated group which had only 10 per cent of their calories from protein, although the total calories represented basal diet plus 100 per cent.

TABLE IX

Stair Climbing Test. The Per Minute Differences Between Resting (Sitting) Pulse Rate and the Pulse Rate at 5 to 35 Seconds and 60 to 90 Seconds After Test. The test Required The Patients to Climb Two Flights of Stairs (44 Steps, 6½ Inches Each) in 35 Seconds

Group Number	Management	Postoperative Average								
		Preoperative Average			2nd Day			3rd Day		
		Resting Pulse Rate	5-35 Seconds	60-90 Seconds	Resting Pulse Rate	5-35 Seconds	60-90 Seconds	Resting Pulse Rate	5-35 Seconds	60-90 Seconds
XII	B +20%, 40% protein, tube fed. Ambulation	77	+25	-2	90	+23	-3	82	+23	-9
VI	B +20%, 15% protein, ambulation	76	+33	+5	87	+42	+7	81	+38	+1
XIII	B +100%, 10% protein, no ambulation except with test	90	+28	0	103	+33	+6	96	+33	+7

Minus indicates less than resting.

POSTOPERATIVE CONVALESCENCE

Step-up Test.—This test is not considered satisfactory for use in postoperative convalescence because of the severe strain inflicted on an abdominal wound by rapidly stepping up and down. However, it was used in three groups of patients having herniotomy, although the test was not used postoperatively until the 7th or 11th day. The control group (non-ambulated basal diet plus 20, 15 per cent protein) showed a greater increase in pulse rate than the shot-gun group (ambulation, supplements, basal diet plus 100 per cent, 20 per cent protein); it showed a less pronounced increase in pulse rate than the group having basal diet plus 20 per cent, 15 per cent protein, spinal anesthesia and only slight ambulation.

Change in Body Weight.—It is agreed that change in body weight is a very crude expression of physical condition, but the degree of shift in either direction may be a fairly accurate index of the efficiency of a certain regime when other factors remain constant. Unfortunately, the weight figures for our control group (II) are not available but Group IV is identical except that spinal anesthesia was used instead of ether. The weight loss in this group was 0.338 kg. per day for the 6 postoperative days, representing the greatest weight loss of all groups studied. (See Table X.) The smallest weight

TABLE X

Average Weight Loss From Day of Operation to Day of Discharge From Hospital (6 to 8 Days)

Group Number	Management	Average Daily Weight Loss (Kg.)
III	"Shot-Gun," basal diet +100%, 20% protein. Supplements. Ambulation	0.033
VI	Basal diet +20%, 15% protein ambulation	0.126
XII	Basal diet +20%, 40% protein. Tube fed. Ambulation	0.133
VII	Basal diet +20%, 15% protein. Tube fed	0.185
VIII	Basal diet +20%, 15% protein supplementation	0.227
XI	Basal diet +20%, 40% protein, tube fed	0.306
IV	Basal diet +20%, 15% protein. Spinal anesthesia	0.338

loss was 0.033 kg. per day, occurring in the shot-gun group (basal diet plus 100 per cent 20 per cent protein, supplements and ambulation), which received high caloric intake and ambulation.

Groups XI and XII received the same treatment throughout except that the latter group was ambulated and the former was not; the weight loss in the ambulated group averaged only 0.133 kg. per day whereas the loss in the non-ambulated group was 0.306 kg. per day. Some of the other comparisons in Table X are not quite so decisive, but there is little doubt but what ambulation minimizes weight loss postoperatively.

Miscellaneous Tests for Circulatory Efficiency or Physical Fitness.—*Vital Capacity* was determined preoperatively and on the 7th and 11th postoperative days in three groups of patients having herniotomy but no significant difference was detected in the preoperative and postoperative figures. The *Strength of Hand Grip and Endurance Time* using the Smedley dynamometer was performed in several groups of patients having herniotomy but no significant difference was detected preoperatively and postoperatively; in patients with cholecystectomy there was a slight decrement in strength of hand grip and endurance, but it was so slight that the test was considered of little value. The unmodified *Flarimeter test* revealed little information except a poorer postoperative performance in the older patients and in several instances dizziness occurred which was not apparent preoperatively.

PSYCHOMETER TEST.—Early in our investigation it became apparent that such tests as steadiness of hand, speed of tapping, simple choice reaction time and coordination time were of little or no value; consequently they were abandoned.

RENAL TESTS.—Various renal tests, such as the phenolsulphonphthalein test, urea clearance, and specific gravity were conducted on numerous patients with herniotomy, but since they revealed very little difference between preoperative and postoperative findings, they were discontinued early; other tests might be of value.

EVALUATION OF PROTECTIVE MEASURES USED.—*Effect of Ambulation.*—Ambulation appears to have a definitely beneficial effect on the nitrogen balance as illustrated in Table V and previously discussed. For example, in two groups of patients having herniotomy who had the same diet (bare maintenance) and treatment except for ambulation, the group having ambulation had a smaller negative nitrogen balance than the group not ambulated. When the diet was increased and all other factors kept the same, the group of ambulated patients had a greater positive balance than the nonambulated group. However, ambulation is unable to maintain nitrogen balance if the dietary intake is lowered significantly. For example Groups VI (ambulation) and VII (no ambulation) were given a basal diet plus 20 per cent, with 15 per cent protein; the former was ambulated and the latter was not. The only difference in the dietary intake was during the first 4 postoperative days, during which time the ambulated group received only intravenous alimentation on the day of operation and 1/4, 1/2, 3/4 and 4/4 diet during 4 postoperative days respectively, whereas the nonambulated group received a full dietary intake (by tube) each day. The negative balance was 13.8 Gm. for the 6-day period in the nonambulated group (VII) compared to 21.3 Gm. in the ambulated group (VI), thus indicating the importance of adequate food. (See Table V.)

As indicated in Table I, the scores in the tilt-table test show a much better performance in the ambulated patients.

The results of the push-up tests are also slightly suggestive that ambulation during postoperative convalescence improves the cardiac or cardio-muscular reserve. In this series (see Table III) the non-ambulated (modified ambulation) group showed a greater postoperative increase in pulse rate after exercise than did any of the other three groups which were ambulated.

Ambulation appears to exert a definite effect on conservation of weight postoperatively, particularly when food intake and protein content are adequate or nearly so. When the figures on effect of ambulation and other factors as related to weight loss are submitted to actual statistical analysis it appears that ambulation is more important than high intake of food or protein individually or collectively, in maintaining postoperative weight of patients having herniotomy (See Table X).

Considering the arrangements of groups it is difficult to draw conclusions as to the effect of ambulation on liver function. However, it is obvious that the effect is not very significant; hepatic impairment may be slightly reduced. For example, Group VI and Group II (See Table I) were treated the same except that Group VI was ambulated. In this group the urobilinogen excretion was 61 per cent of normal compared to 60 per cent of normal in the non-ambulated group.

EFFECT OF TYPE OF ANESTHESIA.—The amount of urobilinogen excreted postoperatively is definitely greater after ether anesthesia than after spinal. For example Group II (control) and Group IV had exactly the same treatment (see Table I) except that the former group had ether and the latter group had spinal anesthesia for their operation (herniotomy). In the control patients the average daily postoperative excretion had increased to a point where the preoperative level was only 60 per cent of the postoperative level, whereas the increase in excretion in the spinal group was definitely less, i.e. the preoperative level was 86 per cent of the postoperative level. Group V was treated the same as Group IV except that the former had modified ambulation. There was no increase postoperatively in this group (IV) over the preoperative level, indicating that spinal anesthesia and modified ambulation together had completely abolished the decrement in liver function.

However a study of figures on bromsulphalein excretion, nitrogen balance and tilt table response reveals no significant difference in the effect of ether anesthesia as compared to spinal in herniotomies.

In cholecystectomy the hepatic impairment after operation was greater than after herniotomy but the difference between patients having ether and those having spinal anesthesia was not of statistical significance.

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EFFECT OF HIGH PROTEIN DIET.—Group VII and Group XI are suitable for this study in so far as all factors were the same except that the diet in the former group contained 15 per cent protein compared to 40 per cent in the latter. Judged by the urobilinogen test, the postoperative hepatic insufficiency was significantly less in patients receiving high protein diet. From the standpoint of figures alone (Table I) the bromsulphalein test indicates less hepatic insufficiency in the group of patients having only 15 per cent protein; however, when the figures are subjected to statistical analysis no significant difference can be demonstrated. The push-up test and the stair-climbing test (particularly the latter) show a distinctly better performance in the patients with 40 per cent intake of protein (Group XII) compared to that in patients with 15 per cent protein intake (Group VI). However, there is a second difference in the treatment of the two groups, namely, the fact that the patients with high protein intake also had maintenance of full diet during the first 4 postoperative days, whereas the patients with 15 per cent protein had no tube feeding on the day of operation, and $1/4$, $1/2$ and $3/4$ diet for the first 3 postoperative days respectively. However, it should be stated that after several days all groups are back to normal.

There was a positive nitrogen balance of 9.6 Gm. (for a 6-day period) in patients receiving a diet with 40 per cent protein compared to a loss of 13.6 Gm. in the patients receiving a diet with 15 per cent protein. The tilt-table test revealed no significant difference between the two groups.

EFFECT OF HIGH CALORIC INTAKE.—To determine the efficiency of high caloric intake in elimination of decrements, postoperatively, the best comparison is between Groups VII and XIII, since both groups were tube fed a diet containing the same number of grams of protein per gram of body weight; the difference in the treatment of the two groups is the fact that the total dietary intake in Group VII was basal plus 20 per cent, compared to a diet equal to basal plus 100 per cent in XIII; the increase in calories in Group XIII was derived solely from carbohydrates and fat. The performance of the patients in Group XIII was inferior to that of Group VII in all of the four major tests (See Table I). This indicates that a food intake as high as 100 per cent above basal requirements is distinctly detrimental, at least if the actual amount of protein per kg. of body weight remains the same. We have no explanation for this phenomenon except that the increase in amount of fat might be considered very deleterious. Other experiments indicate that if the percentage of protein is increased, performance is improved by increasing caloric intake.

EFFECT OF MAINTAINING FULL DIET DURING THE EARLY POSTOPERATIVE PERIOD.—Since the conventional dietary management of patients with abdominal operations consists of no oral feeding on the day of operation and perhaps $1/4$, $2/4$, $3/4$ and $4/4$ diet for the first 4 postoperative days respectively, we conducted numerous experiments with this diet, comparing results with patients having a full diet (by tube) during this period.

A comparison between Group VII and Group II yields data on the value of full diet during the early postoperative period since each group had the same treatment and diet (basal plus 20 per cent, 15 per cent protein) except that the former group had a full diet during the first 4 postoperative days whereas the latter had no oral intake the day of operation and $1/4$, $1/2$ and $3/4$ of full diet, respectively, during the first 3 postoperative days. The patients having full diet during this postoperative period had a better performance score with all 4 tests. The marked difference between the final rank (5 compared to 11) of the two groups can be explained only by one factor, namely, the difference in dietary intake during the day of operation and the first 3 postoperative days. The importance of a basal caloric intake during the early postoperative period is thereby strongly emphasized.

SUMMARY

We have conducted numerous physiologic tests on 92 patients having herniotomy and 10 patients having cholecystectomy. Of eight or nine liver

function tests studied, the urobilinogen and bromsulphalein tests were found the most valuable, at least in our studies. Practically all patients showed impairment of liver function for two to five days following operation; this decrement was greater in the cholecystectomy patients than in the herniotomy patients; it was increased considerably by numerous complications (See Table II). The impairment was less after spinal anesthesia than after ether. In general, this impairment could be prevented by a high protein diet or ambulation (except in the presence of complications).

Studies on nitrogen balance revealed a negative balance postoperatively except when the diet was increased to a level (with increased protein content) above the average postoperative diet. Ambulation had a distinct sparing effect on nitrogen but an increase in the protein content above a 15 per cent level was necessary before a positive nitrogen balance was achieved. Spinal anesthesia had no sparing effect on nitrogen, but in the urobilinogen test showed less hepatic impairment after spinal than after ether anesthesia.

Serum total proteins showed no significant change after herniotomy, but after cholecystectomy there was a definite decline in the serum albumin which was maximum on the 11th day.

There was a definite decrease in the cholesterol and cholesterol esters in the cholecystectomy group, but the decline was too slight in the patients with herniotomy to be of statistical significance except on the third postoperative day.

The tilt-table test was considered to be of definite value in estimating speed of convalescence. The tilt-table scores were much improved by ambulation. Diet appeared to have less effect, although patients with a diet of basal plus 20 per cent with 40 per cent protein had a better score than patients with a diet of basal plus 100 per cent with 15 per cent protein.

Preliminary experiences with a test combining and modifying the flarimeter and Flack test are very encouraging, particularly since the test is a simple one requiring very little time and experience on the part of the operator. During the period of blowing, the pulse rate is elevated and the blood pressure decreased; immediately after the test, the blood pressure rises sharply for a very short time. With this test normal response was not regained before the 10th or 12th day.

In the push-up test (performed on herniotomy patients only) the best scores were made in two groups which were ambulated, one having a diet consisting of basal plus 20 per cent with 40 per cent protein and the second having a diet consisting of basal plus 20 per cent with 15 per cent protein (Table VIII). A third group which likewise was ambulated had an inferior score presumably because of a high food intake and supplements.

In the stair-climbing test the best scores were obtained in the group of patients with basal diet plus 20 per cent, with 40 per cent protein, and ambulation (Table IX). The score was not as good when the protein content was decreased to 15 per cent even though the caloric intake was the same and the patients were also ambulated. The score of the non-ambulated group was

still lower, even though a diet of basal plus 100 per cent (with 10 per cent protein) was given.

Certain conclusions about dietary intake can be drawn. In general, the best performances were obtained when a high protein diet was given. A high caloric intake itself did not improve the test performances; in fact, it appeared distinctly to be detrimental to performance. When a full diet is given every day postoperatively, performance scores are better than when the conventional diet of $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$ and $\frac{1}{4}$ dietary intake is given during the first four post-operative days respectively.

In general, ambulation had a beneficial effect on the scores of all tests, except the urobilinogen test, which alone revealed no difference between ambulated and non-ambulated patients.

REFERENCES

- 1 Ries, E.: Some Radical Changes in After Treatment of Celiotomy Cases. *J. A. M. A.*, **33**, 454, 1899.
- 2 Rusk, H. A.: Army Air Corps' New Convalescent Program. *J. Indiana M. A.*, **36**, 127, 1943; Army Air Forces Convalescent Training Program. *South. M. J.*, **38**, 12, 1945.
- 3 Karpovich, V., Lt. Col. M. P. Starr and Capt. R. A. Weiss: Physical Fitness Tests for Convalescents. *J. A. M. A.*, **126**, 873, 1946.
- 4 Johnson, R. E. and S. Robinson: Selection of Men for Physical Work in Hot Weather, Report 16. Com. on Med. Res. of O. S. R. D., Harvard Fatigue Laboratory, Feb. 15, 1939 (Harvard test).
- 5 Powers, J. H.: The Abuse of Rest as a Therapeutic Measure in Surgery; Early Post-operative Activity and Rehabilitation. *J. A. M. A.*, **125**, 1079, 1944.
- 6 Shafer, P. W. and L. R. Dragstedt: "Early Rising" Following Major Surgical Operations. *Surg. Gynec. and Obst.* **81**, 93, 1945.
- 7 Leithauser, D. J.: Confinement to Bed for Only Twenty-Four Hours After Operation. *Arch Surg.*, **47**, 203, 1943. Early Ambulation, Springfield, Ill., Charles C. Thomas, 1946.
- 8 Elman, R. and J. T. Akin: A Design for Surgical Convalescence. *ANNALS OF SURGERY*, **122**, 716, 1945; R. Elman, D. D. Weiner and E. Bradley: Intravenous Injections of Amino Acids in Postoperative Patients, *ANNALS OF SURGERY*, **115**, 1160, 1942.
- 9 Burch, J. C. and H. C. Fisher: Early Ambulation in Abdominal Surgery. *ANNALS OF SURGERY*, **124**, 791, 1946.
- 10 Cuthbertson, D. P.: Postshock Metabolic Response. *Lancet*, **1**, 433, 1942. Observations on Disturbance of Metabolism Produced by Injury to Limbs. *Quart. J. Med.*, **1**, 253, 1932.
- 11 Keys, A.: *Bumed News Letter*, **5**, 14, 1945.
- 12 Co Tui, Wright, A. M., J. H. Mulholland, V. Carabba, I. Barcham and V. J. Vinci: Studies on Surgical Convalescence. *ANNALS OF SURGERY*, **120**, 99, 1944.
- 13 Ivy, A. C. and M. I. Grossman: Gastro-intestinal Functions During Convalescence. *Fed. Proc.*, **3**, 236, 1946.
- 14 Stafford, G. T., H. B. DeCook and J. L. Picard: Individual Exercises. New York, A. S. Barnes and Co., 1935.
- 15 Taylor, H. L. and Josef Brozek: Evaluation of Fitness. *Fed. Proc.* **3**, 216, 1944.

DISCUSSION.—DR. CHARLES C. LUND, Boston: In the first place, Doctor Cole should be congratulated on the tremendous amount of hard work that has gone into this study. Anyone who has had experience with metabolic studies in patients has a great admiration

for one who can run such studies in so large a group. I had the good fortune to see the manuscript that Doctor Cole summarized at this meeting, and had the opportunity to study it at my leisure. He has covered so much ground in a few minutes that I am going to emphasize some of the points.

In the first place, he speaks of a "shotgun" complete diet. His paper lists a long list of supplements, all the well-known vitamins in large doses, starting with K and C. riboflavin, and so on, down to some of the cruder forms like liver extract and some of the amino acids considered important in metabolic work. The last table he presented was concerned with weight loss. Many surgeons do not take much consideration of any metabolic upset if relatively slight, but these hernia patients were protected by probably a better than average hospital diet and the loss of weight, while not spectacular, was real. It amounted to six or seven pounds loss in a week, with or without ambulation. When he gave a double diet and ambulation together, he essentially eliminated the loss.

This emphasizes the point Elman made in more serious operations, that there was a very serious metabolic upset.

I was surprised that he found as great a decrease in serum albumin following operation, as 25 per cent in patients under ether. With spinal anesthesia there is a loss, but not as much. Everything we can do to keep patients as nearly normal as possible at the time of operation and immediately afterward, is being shown by more and more investigators to be the proper attitude for the surgeon today.

DR. WILDER PENFIELD, Montreal: I think what Doctor Cole said applies to many different types of surgery. My associate, Doctor Cone, and I have found it particularly important to get patients out of bed early after removal of intervertebral disks, because it seems to promote fusion or fixation of the two vertebrae. Weight upon the vertebral column obliterates the intervertebral space.

I should like to ask Doctor Cole a question in regard to terminology, particularly as I know him to be a scholar as well as a scientist. The question refers to the term ambulation. For a new conception it is often wise to employ a new or little used word. But he should indicate to us its correct usage. The verb ambulate, for example—is it intransitive, or does the doctor ambulate the patient? Is it correct to make it an adjective and speak of the ambulated patient?

DR. FRASER N. GURD, Philadelphia: Doctor Cole was kind enough to give me access to his material yesterday. When I told my chief, Doctor Ravdin, that I considered it a significant contribution, he suggested that I step up here and say so, which it is my pleasure to do. The work of Doctor Cole and his associates is closely related to that being done at present, under Doctor Ravdin at the University of Pennsylvania, on the factors affecting the regeneration of liver substance. There can be little doubt that the absolute protein content of the liver is the best measure available of effective liver size. On the relation of diet to the liver protein, Kosterlitz of Aberdeen has stated recently that the amount of cytoplasmic material present in the liver is directly proportional to the logarithm of the casein intake. Dr. Harry M. Vars and I have done some work on this facet of the problem of liver regeneration.

We have prepared rats for 14 days on a protein-free diet, then subjected them to 70 per cent hepatectomy. In a standard recovery period we have measured the amount of new liver protein being formed and also the nitrogen balance. Postoperatively, we have fed a variety of diets, starting from the base line of a protein-free diet both before and after operation. A certain important amount of liver protein is restored even on a protein-free diet, and this amount appears irreducible by any degree of dietary restriction including complete starvation. We have added to the postoperative diets casein at varied levels and other proteins of different biologic values. With dietary protein added, the basal regeneration obtained on the protein-free diet is sharply increased. We have found the closest correlation between the amount of new liver protein formed and the net nitrogen balance. That is to say, those animals eating the smallest amounts of useful protein, and

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exhibiting an unfavorable nitrogen balance, have shown relatively little liver protein regeneration. But by increasing the dietary protein, in proportion to the degree to which the nitrogen balance was strengthened, so has the liver protein been restored. One must emphasize the nitrogen balance rather than the nitrogen intake, because we have shown that the ingested protein favors liver recovery only to the extent to which it remains in the body. The nitrogen balance is the resultant of many influences which are difficult to control independently, but which Doctor Cole has attempted to control. Among such influences are many dietary and environmental factors, stresses like infection, and perhaps the elimination of total physical disuse by getting patients out of bed.

Although it will be extremely difficult to prove such a thesis in the human, I feel that what Doctor Cole is probably measuring is the absolute amount of functional liver cytoplasm. We have definite quantitative measurements of it in the rat, but until we know of a way to measure the total mass of the liver *in vivo* in the human, we are obliged to estimate it by indirect measurements such as Doctor Cole has brought forward.

DR. WARREN H. COLE, Chicago (closing): First I want to thank Doctors Lund, Penfield and Gurd for the very interesting points they brought up in their discussion. From two viewpoints I am much interested in the point which our worthy English scholar, Doctor Penfield, brought up regarding the definition of ambulation. True enough, the meaning of ambulation is extremely varied in the minds of many people. Some doctors are of the erroneous opinion that if the patient is sitting up on the side of the bed he is being ambulated, but he is not; a patient may easily develop a thrombus of the veins of the leg while sitting in this position. The patient must walk about. In our ambulation regime we have added exercises which involve practically all the muscles of the body. I do not consider sitting in a chair to be part of ambulation. Regarding the second part of Doctor Penfield's question—when can ambulation be used as a noun, verb, adjective, etc.? The dictionary allows us considerable liberty in that respect, but if enough people continuously use a certain word not in the dictionary, it will finally be placed in Mr. Webster's dictionary. In other words, usage constitutes law in that respect.

I heard someone ask about patients climbing stairs on the first or second day postoperatively. Obviously, while patients are doing this someone must accompany them. Some of these patients were on the ambulation regime, being given extensive exercises. Others were given no exercises and were kept in bed except during tests; they were classified as non-ambulatory although they did receive some exercise in their test. We did not use the step-up tests of the Harvard type. Although the step-up test is a fairly good test for determining rate of convalescence, I am firmly of the belief that it is too strenuous to use in the first few days after a major operation.

ERRATUM

In the announcement concerning the Editorial Board of *ANNALS OF SURGERY* in the July issue, the biographical note for Dr. Michael E. DeBakey was regrettably in error. We would much appreciate your noting that Dr. DeBakey's title is that of Associate Professor of Surgery at Tulane University School of Medicine rather than Assistant Professor, as stated.

REPAIR OF SLIDING INGUINAL HERNIA THROUGH THE ABDOMINAL (LAROQUE) APPROACH*

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THIS PAPER IS INTENDED to emphasize the advantages of the abdominal approach to the sac and bowel in sliding hernia of the colon. The same mechanism is involved in hernia of the tube and ovary in the female, and the abdominal approach to these organs has the same advantages. Williams.¹ Hernia of the bladder, however, while usually classed as a sliding hernia is involved in direct inguinal hernia and can be handled better from below.

There is still confusion in the minds of many young surgeons and not a few older ones concerning the exact nature of sliding hernia of the colon, this is true in spite of the accurate descriptions of this condition which have been in the literature for many years.

The earliest description of a sliding hernia of the colon which I have found is by Percival Pott² in a chapter on Incarcerated Hernia from his Treatise on Hernia published in 1783. He gives a long and involved description, which undoubtedly was of this condition, though it lacked the concise accuracy of his slightly later colleagues. He was in no way lacking in directness, however, when, expressing his opinion of those who operated on this type of hernia, he said: "But I also know that such accidental successes have emboldened the same operators to commit more than one or two murders in similar cases; and that, from the prevalence of the fashion, some of these rupture-doctors have been largely rewarded, when they ought to have been hanged."

Rutherford³ quotes Scarpa in a good description from his book published in Milan in 1809. Three eminent European surgeons of a slightly later date understood and described this hernia well. Hesselbach was quoted by Samuel Cooper⁴ in 1841. "When in these ruptures of the right side, the cecum, or, in those of the left, the colon, are met with closely adherent to the hinder side of the hernial sac, the adhesion is not to be looked upon as the effect of disease, since it is the perfectly natural connection of those bowels with the peritoneum. On the left side the parts most commonly protruded are the colon and omentum." Liston⁵ in the American Edition of his surgery published in 1838 says: "Sometimes the fixed portions of the colon slip down, their posterior cellular attachments behind being carried into the inguinal canal; a peritoneal sac invests the anterior aspect only." Sir Astley Cooper⁶ in his Lectures published in Philadelphia in 1839 gave as one of the causes of irreducible hernia, "A protruded cecum, in which the intestine adheres by cellular membrane

* Read before the American Surgical Association at Hot Springs, Virginia, March 26, 1947.

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behind, and the sac exists only on the fore part." He had given these lectures for more than 30 years before their publication so he may have been the first to understand and describe this hernia.

Perhaps the reason that sliding hernia is generally so poorly understood is that it is relatively rare. The incidence related to all hernias is about 1.5 per cent; it has been variously reported from 1 per cent to 3 per cent.

The vast majority of reports indicate that the hernia is usually repaired through the inguinal approach. All authors agree that accurate diagnosis



FIG. 1.—Sac open showing sliding colon, muscle splitting incision has been made above internal ring.

cannot be made until the sac is exposed and often not until the sac is opened. It should be suspected when the hernia is indirect, difficult or impossible to reduce completely, difficult or impossible to control by pressure, and has a large defect at the internal ring. Positive diagnosis can sometimes be made by x-ray examination after Barium Enema. Lyons, Brogan, and Sawyer.⁷

The dissection of the sac and colon is attended by some danger of damage to the blood supply of the cecum or colon particularly when the nature of the

hernia is poorly understood by the operator. Demel⁸ reports a mortality of 2.8 per cent of 501 collected cases, the deaths occurred when the colon was resected. Moschowitz,⁹ Lamson¹⁰ and others also called attention to the danger of injury to the wall of the bowel or its blood supply. Reports of operations on sliding hernia were made 100 years ago but of the modern authors the operation of Weir¹¹ began the reconstruction of the mesocolon. He made

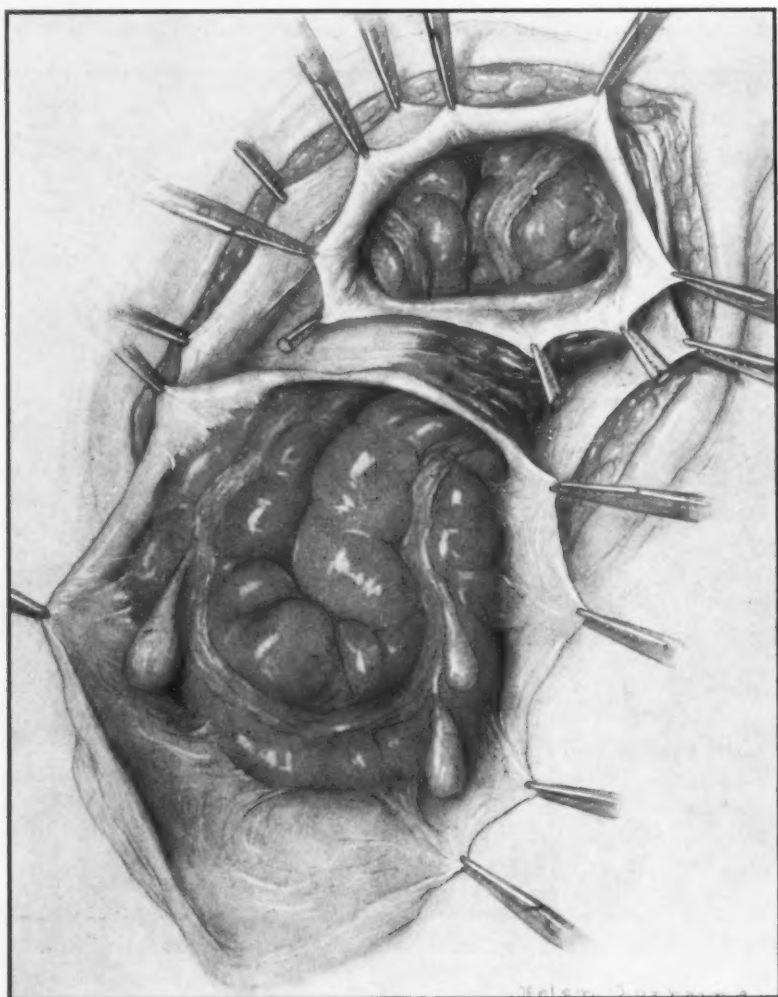


FIG. 2.—Peritoneum open showing colon on left side entering the internal ring.

flaps of the sac and sutured these flaps behind the mobilized bowel, he then closed the reconstructed sac. Hotchkiss¹² did much the same except that he cut away the excess of sac before he sutured the edges to construct the mesocolon. These methods have been modified by Kirchner,¹³ Walton,¹⁴ Bevan,¹⁵ and Burton and Blotner.¹⁶ All of these methods of constructing a mesocolon are

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considered dangerous by Criley¹⁷ on account of possible constriction of the blood supply. He pushes the bowel upward into the abdominal cavity, removes the excess of sac and sutures it. Zimmerman and Loufman¹⁸ do much the same except that they close the sac as high up as possible before dissecting the bowel posteriorly. David¹⁹ introduced another modification in three cases of congenital hernia associated with sliding of the cecum. He divided the sac

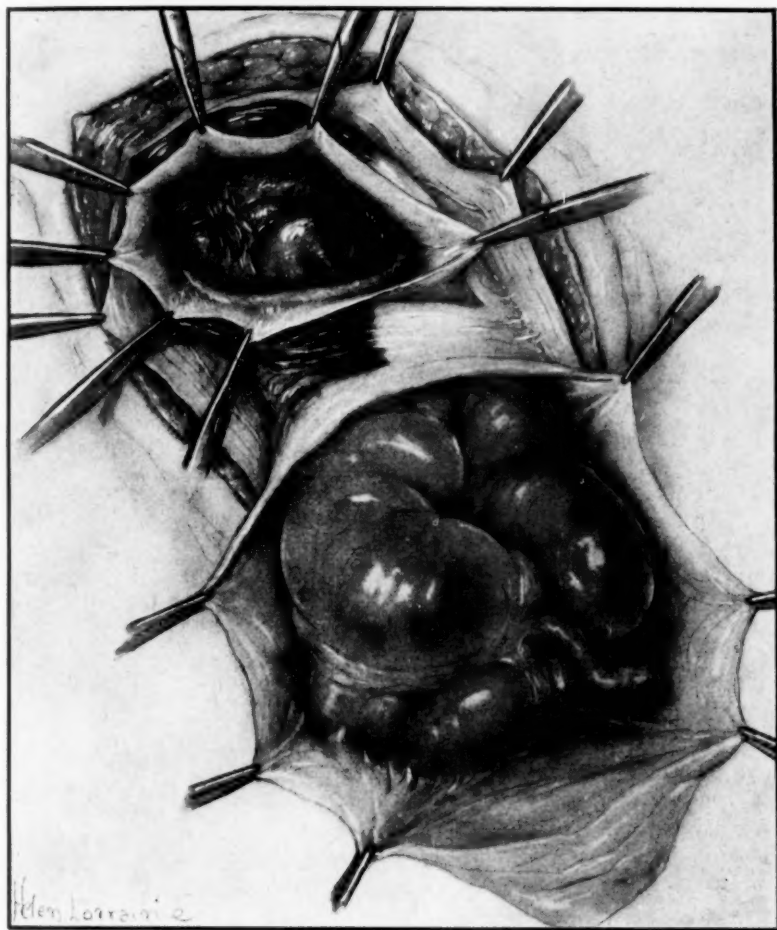


FIG. 3.—Peritoneum open showing cecum on right side entering the internal ring.

transversely above the testicle, then incised the upper portion longitudinally on each side of the cecum, and when the cecum had been returned to the abdomen, sutured the anterior flap behind it.

The slide of the colon probably results from the pull of the complete portion of the sac which doubtless exists before the colon descends and also from the pushing of increased abdominal pressure. The descent is made possible

by a large internal ring and in adults the presence of excess fat is probably another factor.

To accomplish complete reduction of this hernia, that is to replace the colon well into the abdominal cavity away from the internal ring and to completely remove the sac, it would seem logical to reverse both of the stress factors. All of the operations from below combat the pulling but do not correct the push from above. When we can lift the bowel upward through another opening we

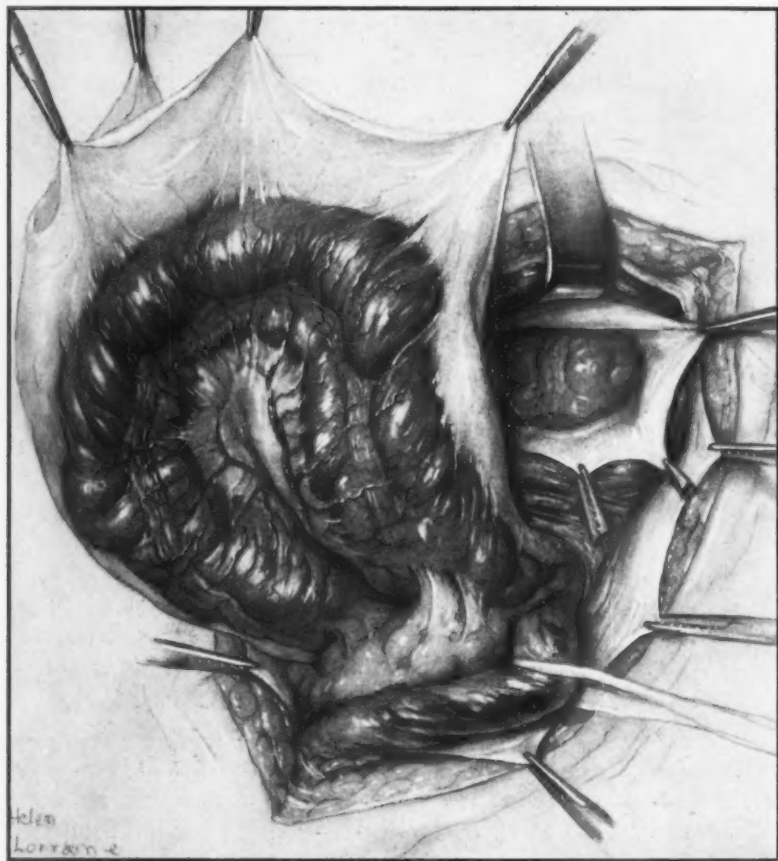


FIG. 4.—The sac and colon have been dissected from the cord and lifted, showing the posterior surface of colon and its blood supply.

accomplish both of these forces and in addition entirely remove the sac and the excess peritoneum. Complete repair of the internal ring is also improved.

The advocates of opening the abdomen above the inguinal canal may be divided into two groups, first those who make this opening for exposure in fixing the colon to the abdominal wall, after the hernia has been repaired in the canal, and second those who use the opening for reduction of the hernia and removal of the sac.

The first report of opening the abdomen above the inguinal canal was

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made by Fiaschi²⁰ in 1907. He considered recurrence due to "the viscous habit of sliding down acquired by that portion of the intestine forming the sliding hernia." He advised a muscle-splitting incision for colopexy as a supplement to the repair from below.

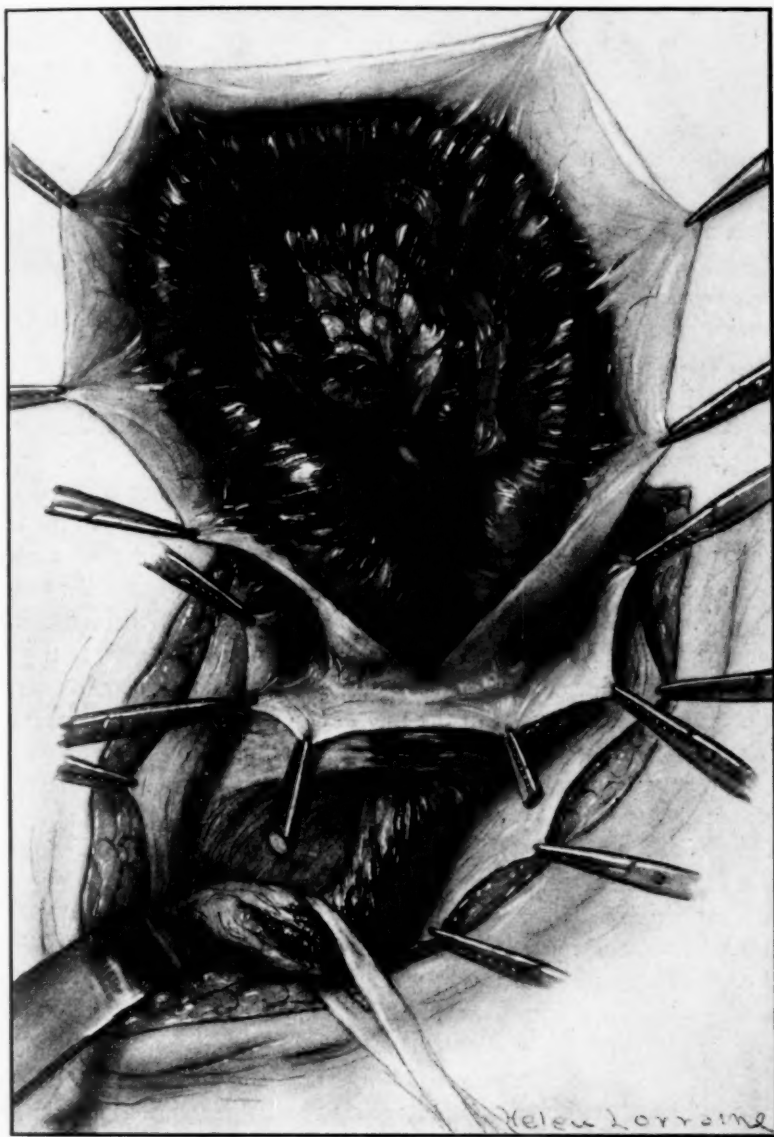


FIG. 5.—The colon has been delivered into the upper wound.

Robins²¹ in 1909 reported the reduction of strangulated inguinal hernia through a rectus abdominal incision; this is probably the first use of the abdominal approach for the reduction of hernia and the removal or closure of the sac.

LaRoque²² in 1919 advocated the approach through a muscle-splitting incision above the internal ring for all inguinal hernias. He elaborated his technic in 1924²³ and described in detail the application of this method to sliding hernia in 1932.²⁴ Williams¹ and Barnes²⁵ who had adopted this method from LaRoque later emphasized its advantages.

Moschowitz⁹ in 1925 advised the use of a muscle-splitting incision for the reduction of small sliding hernias and a ventral incision for the large ones, but he closed the sac remaining in the inguinal canal from below.

Watson²⁶ in 1925 described the use of a ventral incision for colopexy and also advised its use for reduction of large sliding hernias.

Roscoe Graham²⁷ in 1935 reported the use of a rectus incision to reduce the hernia and to suture the mesocolon after dissection of the sac in the canal.

Mackid²⁸ in 1936 described essentially the same method but he overlapped the sac in restoring the mesocolon.

Brown²⁹ in 1943 reported satisfaction in using a technic almost identical with that of LaRoque.

Jacobson³⁰ in 1946 advised the use of this technic in all inguinal hernias.

The advantages of the abdominal approach and particularly the approach through a muscle-splitting incision above the internal ring are not generally appreciated. I have been surprised at the small number of my surgeon friends who use this method. It is indicated also by its complete absence in the text on sliding hernia in *Watson's Hernia*³¹ (1938) and in the chapter on Hernia by Harvey Stone in Lewis & Walter's *Practice of Surgery*³² (1941). In Johnson's *Operative Therapeutics*³³ (1915) a rectus incision for fixation of the colon is mentioned and in Horsley and Bigger's *Operative Surgery*³⁴ (1937) the LaRoque technic is described, but it is not applied to sliding hernia.

A query was sent recently to the members of this and the Southern Surgical Association concerning the use of the abdominal approach to the sac of sliding inguinal hernia. Two hundred forty replies were received; 69 used the abdominal approach, 15 occasionally used it, and 156 did not use it. It would, therefore, seem that the advantages of this technic are not generally recognized and that it would be worth while to present it again.

The usual inguinal incision is made, the external oblique is opened into the external ring, the sac is exposed and dissected from the cord, the sac is opened on its anterior surface and the sliding colon is exposed (Fig. 1). The internal oblique and transversus abdominis are then opened about 1 inch above the internal ring, with care to avoid the iliohypogastric nerve. There is often a fairly firm layer of transversalis fascia at this level which can be used later in the repair. The muscles are retracted and the peritoneum is opened transversely. The contents of the hernia are now revealed from above as they enter the internal ring. Figure 2 shows the double barrel descending or sigmoid colon on the left side and Figure 3 shows the cecum on the right side. The sac is now completely dissected from the cord and the colon is mobilized with care to avoid damage to its blood supply which lies posteriorly (Fig. 4). Traction on the colon from the abdomen draws it and the sac into the cavity.

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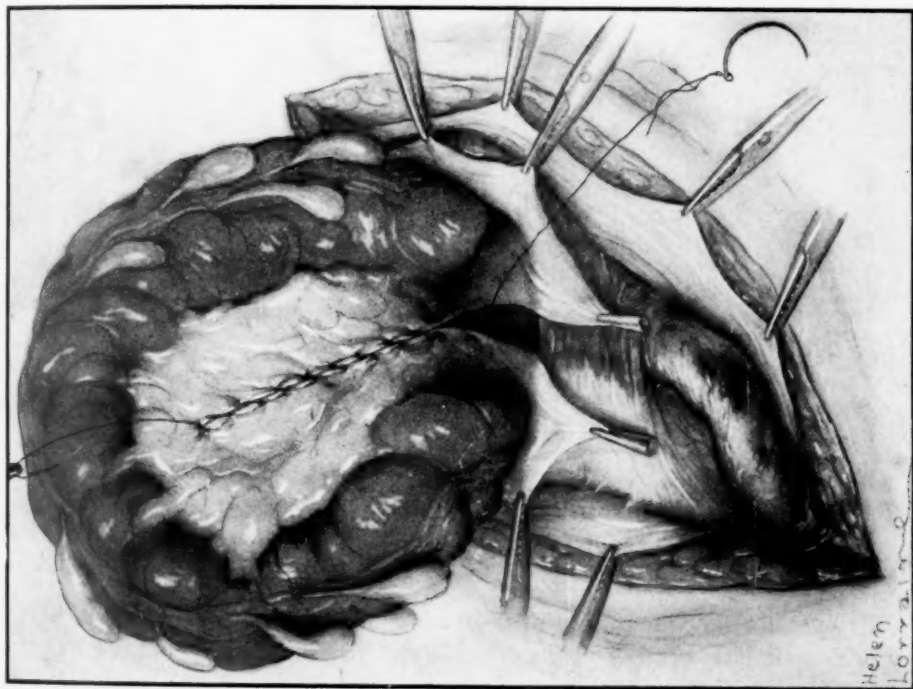


FIG. 6.—Excess peritoneum of sac has been removed, the mesocolon is being reconstructed,

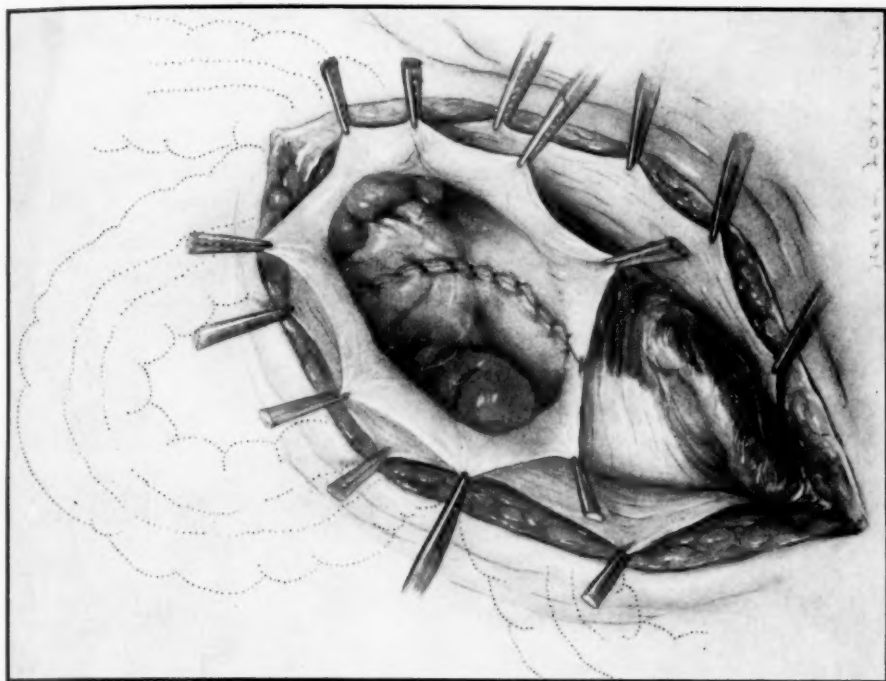


FIG. 7.—The colon has been restored to the abdominal cavity. Note the suture line in the mesocolon extends into the abdominal incision.

It is now obvious that the antero-lateral wall of the sac is the outer leaf of the mesocolon and is continuous with the lower lip of the upper opening into the peritoneal cavity—(Fig. 5). The excess peritoneum is cut away, the mesocolon is closed by suture and the bowel is restored to the peritoneal cavity—(Figs. 6 and 7). The peritoneum is now sutured—it should be noted that the suture line in the mesocolon runs into the lower lip of this incision—(Fig. 8). When the transversalis fascia is present with sufficient strength it can be

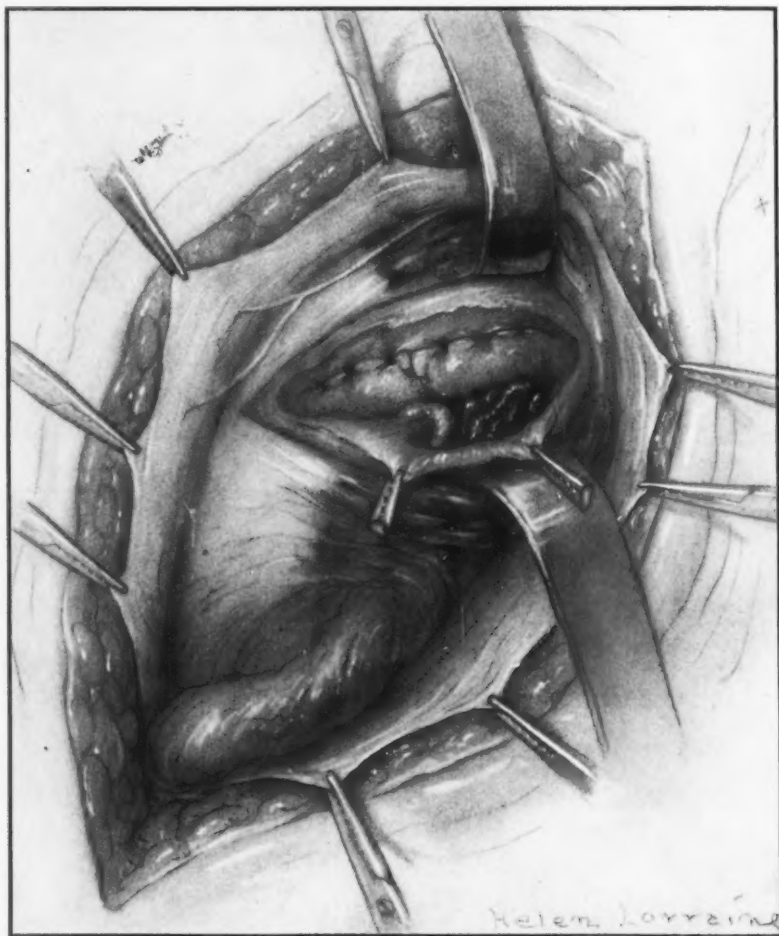


FIG. 8.—The peritoneum has been closed, the transversalis fascia is shown.

sutured so as to make an extra support to the superior portion of the internal ring. The internal oblique and transversus abdominis are then sutured.

The operator now returns to the inguinal canal to make the repair as he may desire. It has been my practice to use the Bassini method, modified by the use of a fascial flap from the rectus sheath or a fascial strip suture from the upper margin of the divided external oblique aponeurosis according to the

size of the defect and the condition of the tissues available for the repair. It is particularly important to have a snug internal ring, some operators have advised complete division of the cord, and other excision of the testicle and cord (Gabb³⁵). The former entails considerable risk of slough of the testicle which may endanger the whole repair, the latter is distasteful to the patient, and conditions which would demand either must be extremely rare.

The advantages of this procedure are:

1. The dissection of the posterior portion of the colon can be completed from above where a better view may be had of the blood vessels to the colon; it is, therefore, easier and safer.
2. The entire sac and excess of peritoneum is removed, this is difficult from below and it is the most important part of any operation for indirect hernia.
3. The mesocolon can be reconstructed in the anatomic position of the bowel.
4. Unusual conditions of the sac and its contents can be more readily recognized and repaired. Garlock.³⁶
5. The colon may be fixed to the abdominal wall if desired.
6. The muscle-splitting incision above the internal ring gives better access to the sac than the rectus incision, it is much more simple and easy, and it is adequate to handle the defect on either side of the body.

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REFERENCES

- 1 Williams, C.: *ANNALS OF SURGERY*, **107**, 917, 1938.
- 2 Pott, Percival: *Chirurgical Works*: ii, 65, London 1783.
- 3 Rutherford, H.: *M. J. Glasgow*, **92**, 113, September 1919.
- 4 Cooper, Samuel: Hesselbach quoted in *Dictionary of Practical Surgery*, New York 1841.
- 5 Liston: Philadelphia, Surgery (American Edition), 1838.
- 6 Cooper, Sir Astley: *Lectures of*, Philadelphia 1839.
- 7 Lyons, C. G., A. J. Brogan, and J. G. Sawyer: *Am. J. Roent.*, **47**, 437, 1942.
- 8 Demel, R. A. (Obst.): *J. A. M. A.*, **78**, 1239, 1922.
- 9 Moschowitz, A. V.: *ANNALS OF SURGERY*, **81**, 330, 1925.
- 10 Lamson, O. F.: *Northwest Med.*, **39**, 175, 1940.
- 11 Weir, R. F.: *Med. Rec.*, **57**, 309, 1900.
- 12 Hotchkiss, L. W.: *ANNALS OF SURGERY*, **50**, 470, 1909.
- 13 Kirchner, W. C. G.: *Amer. J. Obst. and Diseases of Women and Children*, **64**, 5, 1911.
- 14 Walton, A. J.: *ANNALS OF SURGERY*, **57**, 86, 1913.
- 15 Bevan, A. D.: *ANNALS OF SURGERY*, **92**, 754, 1930.
- 16 Burton, C. C., and C. Blotner: *ANNALS OF SURGERY*, **116**, 394, 1942.
- 17 Criley, C. H.: *Surg. Gynec. Obst.*, **31**, 611, 1920.
- 18 Zimmerman, L. M., and H. Laufman: *Surg. Gynec. Obst.*, **75**, 76, 1942.
- 19 David, V. C.: *ANNALS OF SURGERY*, **77**, 438, 1923.
- 20 Fiaschi: *Australasian Med. Gaz.*, 1907.
- 21 Robins, C. R.: *Old Dom. J. Med. and Surg.*, **8**, 5, 1909.
- 22 LaRoque, G. P.: *Surg. Gynec. Obst.*, **29**, 507, 1919.
- 23 LaRoque, G. P.: *ANNALS OF SURGERY*, **79**, 375, 1924.
- 24 LaRoque, G. P.: *Arch. Surg.*, **24**, 189, 1932.
- 25 Barnes, W. P.: *Va. Med. Monthly*, **66**, 395, 1939.

- ²⁶ Watson, L. F.: *Internat. Clinics*, **4**, 155, 1925.
- ²⁷ Graham, R. R.: *ANNALS OF SURGERY*, **102**, 784, 1935.
- ²⁸ Mackid, L. G.: *Canadian Med. Asso. Jour.*, **34**, 269, 1936.
- ²⁹ Brown, R. K.: *Surg. Gynec. Obst.*, **76**, 91, 1945.
- ³⁰ Jacobson, P.: *Amer. Jour. Surg.*, **71**, 797, 1946.
- ³¹ Watson, L. F.: *Hernia*, Mosby, St. Louis 1938.
- ³² Stone, Harvey B.: *Practice of Surgery*, Lewis and Walters, VII, Chapter 9, 1941.
- ³³ Johnson's *Operative Therapeutics*, Vol. 4, p. 72, New York 1915.
- ³⁴ Horsley and Bigger: *Operative Surgery*, Mosby, St. Louis 1937.
- ³⁵ Gabb, H.: *Lancet*, **1**, 554, 1929.
- ³⁶ Garlock, J. H.: *J. Mt. Sinai Hosp.*, **4**, 818, March-April 1938.

DISCUSSION.—DR. ROSCOE R. GRAHAM, Toronto: We are indebted to Doctor Williams for bringing forward this problem of sliding hernia. One is amazed to find that in the reply to the questionnaire which Doctor Williams sent out, there was such a percentage of surgeons who did not use the transperitoneal approach in the repair of sliding hernia.

It is tremendously important that we stress the diagnostic points which are helpful in the preoperative recognition of a sliding hernia, particularly when we are so liberal in allowing the resident staff to operate upon herniae without strict supervision.

We should suspect the diagnosis of a sliding inguinal hernia when there is a history of a long-standing hernia, when a truss which formerly was efficient can no longer be worn because of pain and irritation, and finally the hernia becomes irreducible. Sliding hernia can be confirmed by a barium enema, showing large bowel in the sac. At operation the presence of a large mass, thick, and without a definite margin of a sac, puts one on guard. In our experience it has not been necessary to excise any peritoneum. A withdrawal of the sigmoid or cecum into the peritoneal cavity has shown that the peritoneum presenting in the inguinal canal is peritoneum covering the mesentery of the bowel, and it can be readily closed with a few sutures. The ease, safety and permanency with which one can deal with a sliding hernia by the peritoneal approach makes it undoubtedly the ideal technical procedure.

DR. C. REID EDWARDS, Baltimore: I think Doctor Williams is to be complimented for calling attention to the abdominal approach to this type of hernia. It is a hernia that is turned over frequently to the house man for operation, and the senior man bears considerable responsibility. I am sure you all can recall the older textbooks in which a print of a scrotal hernia appeared; the title was "Scrotal hernia in which the abdominal contents have lost the right of domicile." On the left, the sliding hernia will have the sigmoid; on the right, the cecum and much of the ileum.

A few years ago a Negro was admitted to the hospital with a scrotal hernia descending to the knees. He had made a harness for himself. We thought it wise to investigate the sac before undertaking an operation, and we found the ileocecal valve at the upper level of the patella. That is an exaggerated case, but it shows what can happen in a neglected case. There is no use even thinking of the usual operative procedures. The contents of the abdomen have been out for too long; the viscera have sacrificed the "right of domicile." Any attempt to put that back is likely to damage the circulation to the right and left colon.

In a patient who is excessively fat, it is wise, after proper x-ray, to turn him over to the medical service for weight loss. This man lost 26 pounds and then came to operation. A long paramedian incision was made and it was not possible to pull the contents back into the abdomen. Then an inguinal incision was made, and it was still not possible. So then all structures were divided at the spine of the pubic bone; the entire wall was reflected and, with difficulty, the mass could be turned back into the peritoneal cavity and the structures apposed.

SLIDING HERNIA

I believe it is wise to advocate study by x-ray of all gross sliding hernias, to establish definitely what part of the bowel has descended into the scrotum, and how much risk there will be of endangering the vascular supply to the colon.

DR. WILLIAM L. ESTES, JR., Bethlehem, Pa.: I have been meeting the problem of the sliding hernia from a little different angle and have, therefore, been very much interested in Doctor Williams' presentation. We have been using for the correction of sliding and other hernias a so-called fascia-to-fascia rectus sheath closure. In this operation the sheath of the rectus is split about 1 cm. medial to the margin of the muscle, the entire length of the inguinal canal. This lateral margin of the rectus sheath is sutured with interrupted cotton sutures to Cooper's ligament as originally suggested by Harkins and McVey for the usual Bassini procedure. The second layer for the posterior wall of the canal is then formed by suturing the external oblique attached to Poupart's ligament to the medial margin of the sheath of the rectus, thus giving two layers of superimposed sutured fascia for closure of the posterior wall. The operation is completed by suturing the lateral margin of the external oblique muscle over the cord to Poupart's or the inguinal ligament.

However, an important part of the operation is the correction of any defect of the transversalis muscle before the above method of closure is begun. The defects usually found are orifices of direct herniae, a large internal ring, or a weakness of the muscle close to the pubic spine. These are closed by interrupted cotton sutures.

In the case of sliding hernias we rarely open the sac. The hernia is carefully freed from the structures of the cord and restored to the peritoneal cavity, and the large internal ring is closed with interrupted cotton sutures; the operation is concluded by the above fascia-to-fascia rectus sheath procedure. We have recently studied follow-up results covering three years or more. All patients have been examined personally. Of 119 indirect hernias there was one recurrence; in 56 direct hernias, three; and in 11 recurrent hernias, no recurrence. Of this entire group, 26 were sliding hernias with no recurrence. The over-all recurrence rate, therefore, was found to be 2.2 per cent.

There is, however, a definite possibility of atrophy of the testicle if the internal ring is closed too snugly. We have avoided this by not angulating the cord by suturing too high at the internal ring, and being careful to have an opening at the internal ring at least 1.5 cm. in diameter.

We therefore feel justified in suggesting this method of treatment as effective for sliding hernia, as well as the method Doctor Williams has described.

DR. CARRINGTON WILLIAMS, Richmond, Va. (closing): Doctor Graham and I are almost in entire accord on sliding hernias. I do think there is usually a small sac at the bottom of the mass. Doctor Edwards' large hernia was certainly unique, and proves that there are instances where the abdominal approach is very useful. Doctor Estes' report of non-recurrence is indicative of the fact that abdominal approach is unnecessary; perhaps the Estes repair shop in Bethlehem is better than mine in Richmond, because the only case of recurrence I had was one that looked so easy that I did not use the approach from above.

REPAIR OF MAJOR FACIAL INJURIES*

JAMES BARRETT BROWN, M.D.

ST. LOUIS, MISSOURI

AND

BRADFORD CANNON, M.D.

BOSTON, MASSACHUSETTS

SOME OF THE SALIENT PROBLEMS and some of the methods of repair in caring for patients with major facial injuries are presented here. Including the great numbers seen in military service, the most frequent causes are gunshot wounds, burns, traffic crashes, radiation exposure and freezing. (The defects of congenital origin and those resulting from cancer are of a group dealt with elsewhere.)

The surgeon like the tailor can make no better coat than his cloth and it is well to realize limitations as well as possibilities in attempting major repairs. There is only one original and most surgical restorations are only substitution. Diagnosis is of major importance and includes determination of what tissue has been lost or displaced as well as what distorted function to expect from it.

One often has to hold in abeyance rules that are promulgated for general usage over the body—such as the cutting debridement or packing all wounds open. These two measures were aimed mainly at the prevention of gas gangrene, but this complication is extremely rarely, if ever, seen in the face. On the other hand to do a cutting debridement of the face might needlessly sacrifice a feature—such as an eyelid, whereas these tissues have great recovery power; and to pack open a displaced nose or eyelid is to lose the best chance of repair—which is early.

It has been firmly established that if badly lacerated faces can be restored promptly—that the one single operative procedure can often effect an excellent result. The patient in Figure 1 represents this type of soft tissue injury, with almost no structure left undamaged in the area. By early evacuation and prompt surgical repair—without cutting debridement, or packing the wound open—this patient has had her complete result obtained in the one single operation. Without this early operation as satisfactory result would never have been attained, even with the twenty or thirty operative procedures that would have been necessary.

Pressure dressings on the face—especially, in fresh injuries, are as important as any place in the body. The use of fine, white cotton mechanics waste—now supplied as surgical waste—supplies an excellent medium of pressure—the final pressure of course being obtained with appropriate rolls of bandage. It is interesting that the first use of a pressure dressing recorded is in the

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* Read before the American Surgical Association, March 26, 1947, Hot Springs, Va.

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heiroglyphics, and is in relation to facial wounds. Edwin Smith Surgical Papyrus.

The normal face, among other things, needs protection of the eyeballs, a nose to breathe through and a mouth to allow normal eating. These elements should guide the approach to the problem of repair of the badly injured face



FIG. 1.—Early evacuation and immediate operation. One single operation for complete repair.



FIG. 2.—Use of local tissue in one operation for repair. Saliva turned back down the throat instead of out on chest.

and in the mess of the acute injury such basic philosophy of treatment should not be lost sight of in the face of all the technical details. This statement perhaps may appear trite, but to wind up a severe facial injury repair and fail to obtain an airway for instance, means needless discomfort and possibly permanent loss of normal function.

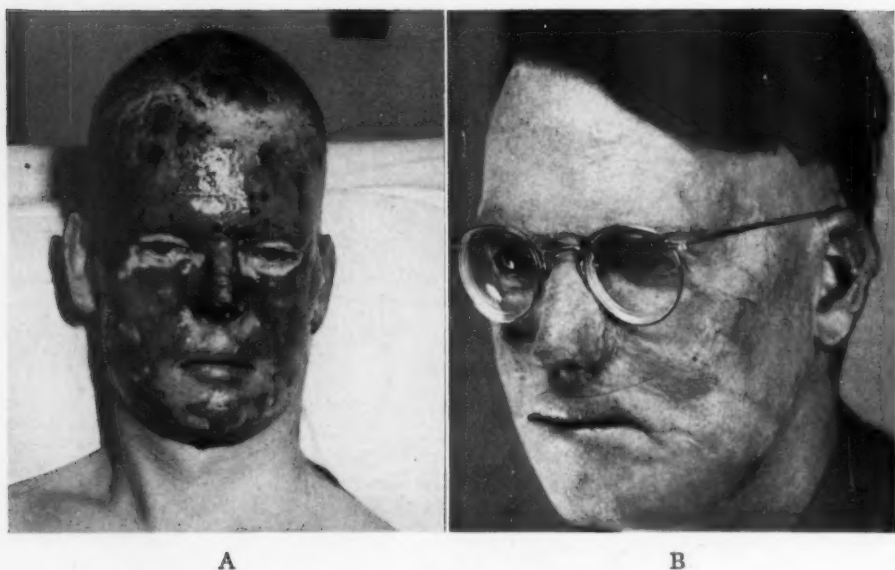


FIG. 3.—Total burn of face, grafted early to obtain healing. Contracted scars and imbedded whiskers dissected out later and full restoration done with free split skin grafts. Forehead, cheeks, lips, chin, eyelids and nose all grafted.

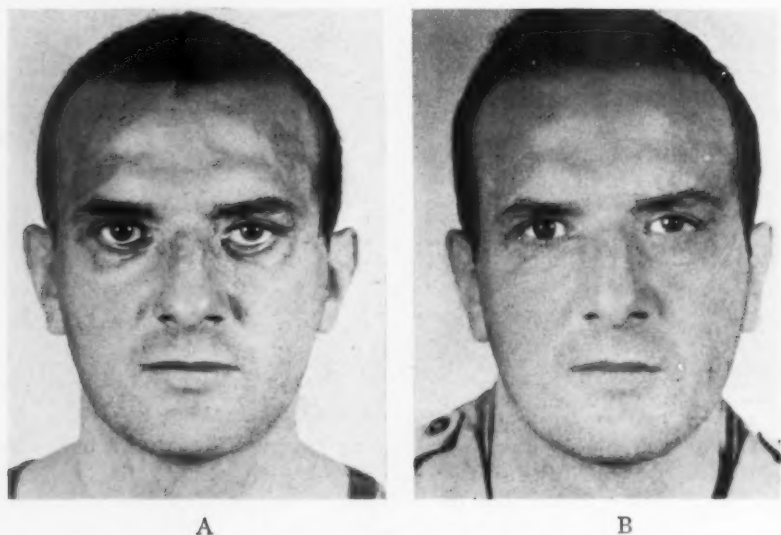


FIG. 4.—Free full-thickness grafts from clavicular region to recover lids after dissection of scar. Two lids done at one operation, no secondary trimming necessary.

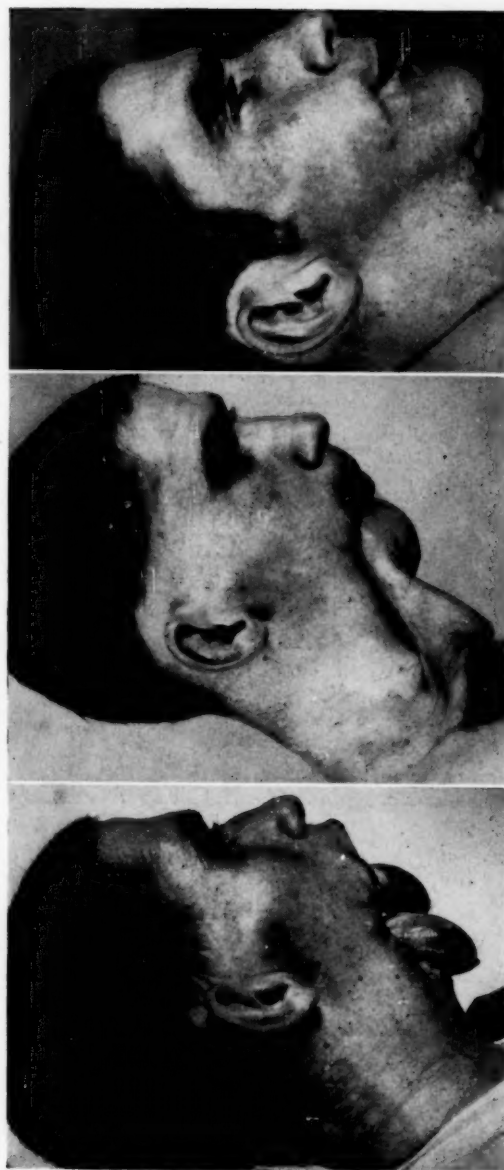


FIG. 5.—Complete loss of chin and surrounding soft tissue, jaw gone from ramus to ramus, tongue fixed out on neck. Restoration with large lined flat flap from chest. Free graft to mobilize tongue, flap defect grafted at time it was used. Single bone graft of entire jaw from stump of ramus on one side to the other, done with single rib.

In carrying out secondary repairs the following considerations and procedures are summarized.

Local tissue is utilized when ever possible to effect repairs. In Figure 2 this is well illustrated with the entire repair being done in one operation and the saliva turned back down the throat rather than out on the neck. This fundamental which includes the use of the Z-flap is almost so obviously to be considered that it is some times not mentioned adequately. All possible local tissue is always used whether additions are made or not. (Figs. 5 and 7.) On



FIG. 6.—Practically total loss of covering of face from freezing. (Early photo courtesy Dr. E. M. Bricker.) (Early grafting done by Doctor Hickey.) Restoration in 18 operations. Almost entire resurfacing of flat surfaces of face with free thick split grafts including orbital region. Whole nose made from flat arm flap and preserved cartilage. Ears made from scalp flaps, cartilage and split skin grafts. (The loyalty of this patient's wife saved him for a normal life and they together are making their way.)

the other hand the method should not be used when it will distort other features or interrupt important nerve supply. One could hardly expect widespread losses from burns about the eyelids and cheeks and nose to be subject for this treatment, and there frequently must be new tissue added.

The ability to add new tissue is the "sine qua non" of the plastic surgeon, and the following necessary instances of supplying new tissue are presented.

Burns require free skin grafts most extensively—free grafts are preferable on flat surfaces to thick flaps, because of finally being more expressive, there being little emotional expression possible through or under a thick flap. Fig-

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FIG. 7.—One of the worst types of composite and compound injury. Restoration with local tissue, free skin grafts and flat flap from arm for nose. Cancellous bone graft for jaw. Cartilage support for nose.

ure 3 represents almost a complete replacement of the skin of the face with free skin grafts, both cheeks, forehead, lips, chin, eyelids, and nose being covered. The skin of the anterior chest wall just below the breast is usually best for the flat areas of the face.

Free full thickness grafts from the clavicular region, have been recently utilized to excellent advantage on the eyelids and nose. The color best matches the face and the function is excellent. The patient in Figure 4 illustrates the total resurfacing of the lids with these grafts without the necessity of any secondary trimming of the edges.

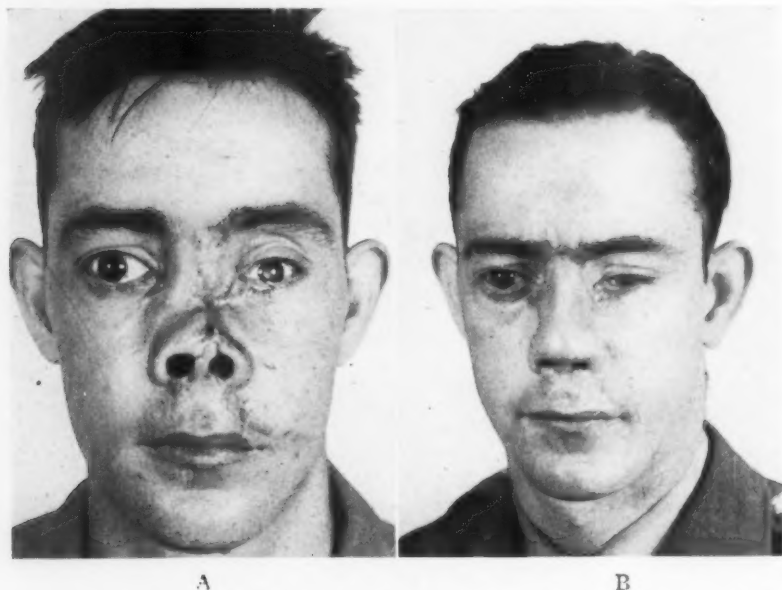


FIG. 8.—Use of distant flap for nose, rather than cut into forehead. Flat flap from arm used. Cartilage for support and final color obtained with permanent pigment injection. Patient has only travel vision.

Total losses of areas as in Figure 5 require flap restoration of the soft parts and finally support for the soft tissue restoration. (The plastic surgeon has to build somewhat backward, putting in the outside or covering first and the support later.) This patient has had a free graft under the tongue to allow movement. Then a lined flat flap from the chest made the chin, lip and floor of mouth. This closed the mouth, turned the saliva back down the throat and permitted his taking food. The flap is a flat one, turned in for lining, not tubed. The defect of its bed is grafted at the time it is used.

Restoration of the jaw has been done as in Figure 5, putting in the entire body with a rib transplant—extending from ramus to ramus. It is planted in the new flap first and then attached to the remnants of the ramus later. The restoration of this patient is far short of his worth and the surgeon's wishes for him but it is adequate for him to follow a normal life.

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Cancellous bone from the ilium is used extensively in jaw replacements and probably gives the best overall chance of healing (Fig. 7).

Freezes of the face are apt to be widely destructive as in Figure 6. This patient has had almost his whole face resurfaced with free grafts including the whole region of the orbit. The nose and both ears have been totally reconstructed.

Noses are usually made from forehead or neck flaps, but as in the above patient (Fig. 6) it has been made from an arm flap. In Figure 7 the nose has also been made from an arm flap as shown—in this patient the forehead was too narrow. In Figure 8 the arm has been used to avoid scarring the forehead. The final color match was obtained in this patient by pigment injection.

Ears are usually made from a local scalp flap, a cartilage transplant and a free skin graft. Both ears on the patient in Figure 6 were made at the same

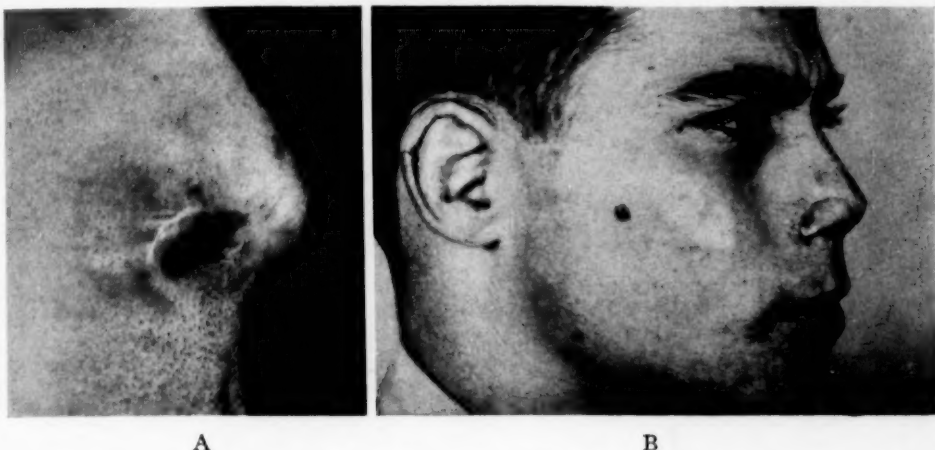


FIG. 9.—Composite free graft of two surfaces of skin and intervening cartilages from ear for nasal reconstruction. One single operation. Repair of ear with scalp flap.

time in three operations (as reported in S. G. & O., February, 1947). If desirable a short tubed neck flap can be added.

Composite grafts of skin and cartilage from the ears have been used extensively for repairs of the nose as shown in Figure 9 and as reported previously in the ANNALS OF SURGERY October 1946 and Surg. Gyn. and Ob. April 1946.

Cartilage is usually used to support noses as in Figures 6 and 7. The transplant is cut in an L-shape in one piece and may be homogenous, autogenous or preserved. Cartilage is also used in chips and grated to fill defects that can be molded into shape and don't require too much support. Cartilage for ears is essential and if the angle of a costal cartilage is available a good shape of an ear may be cut out of it.

As can be noted there is a composite picture of care in the restoration of these patients; the original life saving work just after the accident, the endless

nursing care, and the cooperation and work of the ophthalmologist, the rhinologist and the dental surgeon. The endless detail and dressing care and operative work that is supplied by house surgeons and younger surgeons is recognized as essential for the recovery of these patients.

These patients are still individuals and have all the problems of getting along that anyone does, and they should not be grouped as a class, or given up because of their difficulties. The work often appears endless both for the patient and the surgeon—and the surgeon too well realizes that the best result will be short of his wishes or of what the patient deserves. But slow progress can be made, of lessening the time required in the repair, of improved technical work, and of making good work more easily available through observation, recording and teaching.

DISCUSSION.—DR. LEO ELOESSER, San Francisco: In expressing the universal recognition of these truly dramatic results, I would like to add one word, to say that the prepuce, if available, may be used for making pretty good eyelids. If one circumcises the patient and splits the prepuce part way so as to shape it into the form of a pair of trousers, one leg of this free graft will make an upper lid and the other a lower lid.

MR. H. ECKHOFF, London, England: It is very difficult to know what to say about the paper of Dr. Barrett Brown. We were lucky enough to have Doctor Brown with us once or twice. In the main we carried out these special restorations in the same manner that Doctor Brown has shown you, the only marked difference being in rhinoplasty. The use of the flap from the ear is more common in the States than in England. At East Brinsted, where I did most of my work, we used the forehead almost entirely for these reconstructions. There were of course many cases where that was not possible, cases in which the forehead had been extensively damaged from bombs or by other injuries. In those instances we preferred to use the thoracic pedicle, with the thought that the arm-to-nose position was uncomfortable for the patient. Even when we have completed as much as we can, these people do lack a good deal of what we would like for them. Nevertheless, as you see them in the mass, see them individually and get to know them, you realize how wonderful it is to be able to help them, even to a limited extent.

DR. JAMES BARRETT BROWN, St. Louis (closing): I want to thank Doctors Eloesser and Eckhoff. In replying to Doctor Eloesser's suggestion, the only prepuce grafts we saw on eyelids became so black that we had to remove them and replace them with other grafts. If they would stay light, they would probably be satisfactory.

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